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THE AMERICAN REVIEW OF TUBERCULOSIS

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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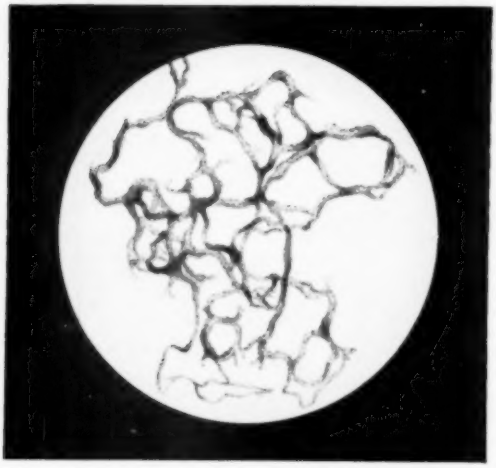

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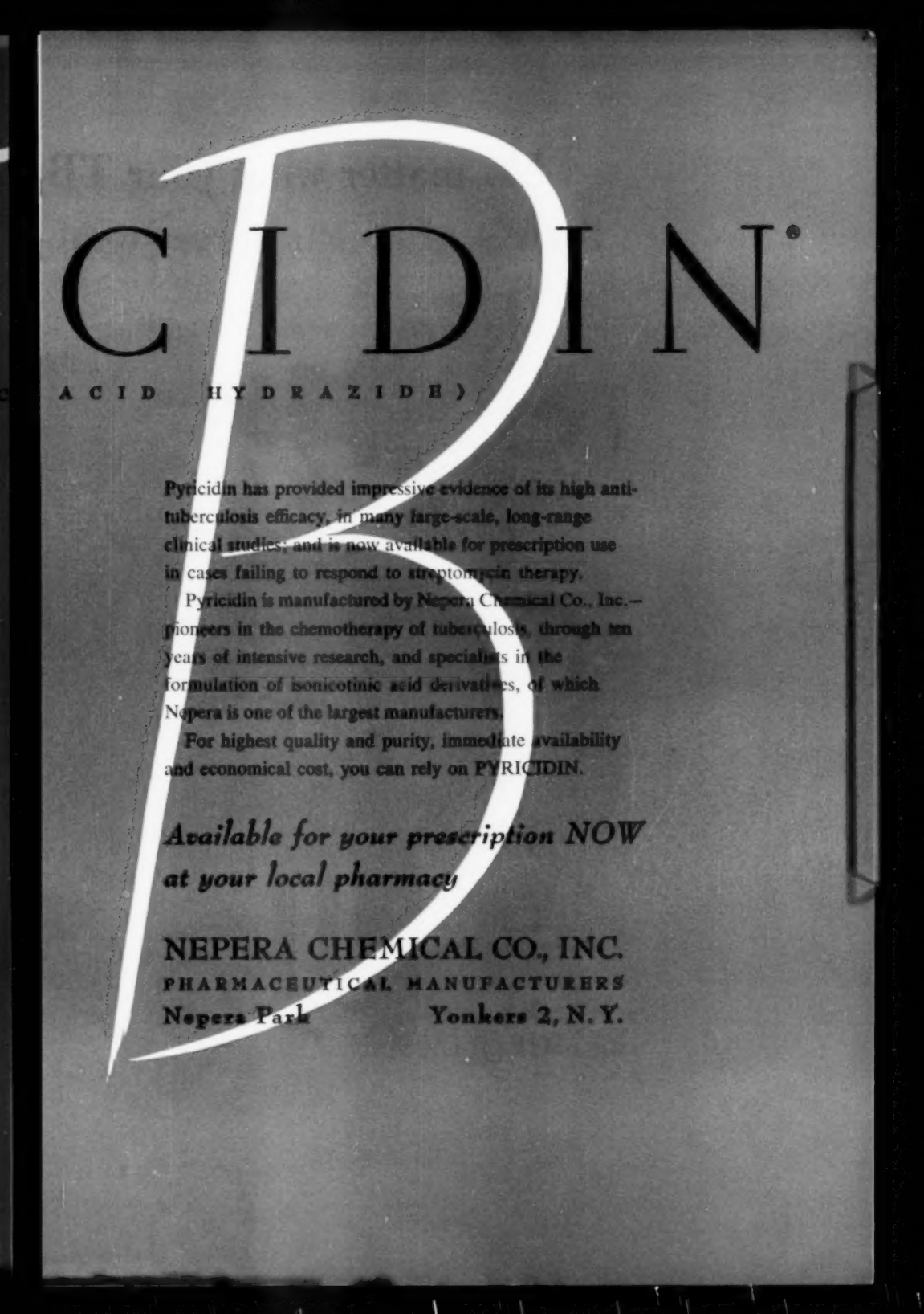
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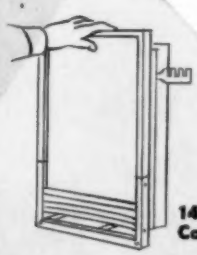

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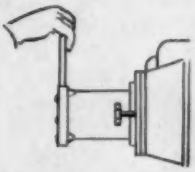

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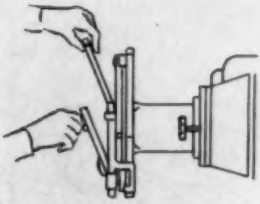

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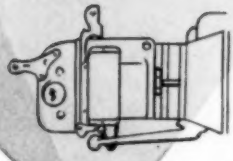

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THE AMERICAN REVIEW
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VOLUME 66 *July 1952* NUMBER 1

INCIDENCE OF PULMONARY TUBERCULOSIS IN A GROUP CONTINUOUSLY OBSERVED AND PERIODICALLY RE-EXAMINED[1]

FERNANDO D. GOMEZ AND ARISTEO A. PIAGGIO

(Received for publication January 7, 1952)

INTRODUCTION

Recognition of the fact that pulmonary tuberculosis frequently develops over a prolonged period of time with few accompanying symptoms, or indeed asymptomatically, and finally becomes manifest clinically in an advanced stage has led to the practice of examining apparently healthy groups. This procedure is considered to be the most effective method whereby the disease can be diagnosed in an early stage when it is of slight extent and can be treated most rapidly and successfully.

Examination of the entire population of a country, however, is not easy to accomplish because of the difficulties inherent in transporting a large part of the population to roentgenographic units. Moreover, there is a considerable financial burden involved in the necessary educational propaganda, the transportation of technical personnel, and the follow-up for diagnostic purposes of that high percentage of examined subjects who require additional studies on the basis of abnormal findings.

In August, 1948, the Honorary Commission for the Antituberculosis Campaign of Uruguay embarked on a mass investigation of the entire population, which terminated in April, 1951. It appears that 40 per cent of the inhabitants, or approximately 850,000 persons, were examined.

From 1939 on, the Institute of Phthisiology and the Department of the Phthisiological Clinic, both of them subsidiaries of the Faculty of Medicine, carried out systematic examinations of apparently healthy persons. They were concerned less with reaching the largest number of persons possible than with carrying out intensive studies.

The Epidemiological Section, which operates with one of these units, made a total of 15,000 to 18,000 examinations each year. This section makes periodic examinations of groups of different social position and varying age, type of em-

[1] From the Instituto de Tisiología y Cátedra de Clínica Tisiológica de la Facultad de Medicina, Montevideo, Uruguay.

ployment, and standard of living. In addition, in order to recognize the incidence of tuberculosis, its type of onset, character of development, and morbidity and mortality rates, this unit has maintained certain social groups under periodic observation since 1939.

The experience in Juan Lacaze, a community of 7,500 inhabitants which has been examined ten consecutive times since 1939, has been reported in different publications. The group observed has included school children and, particularly, employees and workmen assigned to different tasks and industries, such as meat, glass, textiles, et cetera. In repeated routine examinations, the present writers attempted to make an intensive study of the influence of environment, character of work, living conditions during working hours, et cetera on the appearance and spread of tuberculosis among persons who during the rest of the day mingle with others in homes and common places of recreation. Their contacts, although unknown, may be considered, because of their heterogeneity and number, as representative of the environmental and social state of the different strata making up the population of the capital. In the present paper an attempt will be made to record the experience and knowledge gained to date in examining this group which, if not among those investigated for the longest period, nevertheless offers a very important advantage in its stable majority composition of permanent government employees.

In addition, this study includes office employees, shop workers of different kinds, and an important nucleus of others who carry out tasks of permanent character in the street or open air. On the basis of these characteristics, the group may be considered a representative sample of the office and worker population making up the laboring class of the city of Montevideo, which includes one-third of the total population of the Republic. Equally important is the fact that a well-organized medical certifying service was in operation, with a zealous administrative office perfectly adapted to its purpose. This service maintained an amply documented record of absences and health of personnel on the basis of information furnished by a highly efficient and diligent medical unit cooperating with local inspectors charged with the fulfillment of technical instructions.

The State Electric and Telephone Plants, an important autonomous unit, was the group in which the principal efforts were directed to the study here reported. It has a monopoly of these services in the department and city of Montevideo, and in recent years has been incorporating in its structure almost all of these services in other parts of the country. At the end of 1939 the Institute of Phthisiology obtained from the directorate of this organization the necessary authorization to carry out a tuberculin and photoroentgen study of its personnel. A number of difficulties, which need not be enumerated, limited this opportunity to the examination of 851 persons, i.e., approximately one-third of the total personnel of the organization.

Seven years later, the accidental discovery of a case of cavitary pulmonary tuberculosis in the office of the secretary of the directorate and the suspicion of contagion from a working companion excited the interest of the Board of Directors. With the full cooperation of the latter, and particularly with the

perseverance and personal attention of the president of the organization, who put the full weight of his influence on all of the section chiefs, supplemented by the interest and authority of the Medical Office, the examination that year took on a comprehensive character originating with the directors themselves.

The same procedures were followed in the succeeding years with respect to the permanent personnel; the temporary day laborers working on the extension of lines and services and in the large Palace of Light, in which the central offices were located; and the personnel engaged in the electric light and telephone services in other departments of the country in so far as they were incorporated in the organization.

All of these employees, even those from the most distant departments, were required to come to the capital and submit to the examination conducted by the Institute of Phthisiology. The results of tuberculin tests and photoroentgen examinations carried out in these investigations will be set forth and analyzed in the present report.

A fact of fundamental importance should be noted, viz., that the writers took into account, not only their own findings in five annual investigations, but also the data assembled in the archives of the Medical Office. In the latter records, all matters pertaining to health which transpired during the period between investigations are recorded, including illnesses that led to temporary absence, prolonged leave, or compensation based on loss of health. This Office, moreover, sends to us for diagnosis all sick or presumptively ill persons with pulmonary abnormalities or suspected tuberculosis, detected at any time during the year.

METHODS

Type of Examination Instituted Periodically

The first investigation was carried out at the end of 1939 and the beginning of 1940. This consisted of tuberculin tests and chest photoroentgen film examinations. A unit composed of two physicians and four technicians, with a portable photoroentgen apparatus and all the necessary office and medical material, was transported in a series of moves to the most distant dependencies of the organization. Each person present for examination was registered, with notation of personal and individual data, personal antecedents, and family contact with tuberculosis and other diseases of the respiratory system. A serial number was given to each registrant. The first procedure was a cutaneous test, which was performed by placing on a previously disinfected forearm one drop of full-strength Koch's tuberculin from the Institute of Experimental Hygiene and making a scratch 1 cm. long through the drop with the point of a needle. The cutaneous reaction was interpreted after forty-eight hours. Papular infiltrations, 3 mm. or more in diameter, were considered positive. In the event of doubtful or negative reactions, a second test was made immediately by injecting intradermally 1 mg. of tuberculin (0.1 cc. of a one per cent solution in 0.5 per cent phenolated distilled water). The reaction to this, in turn, was interpreted forty-eight hours later and every papular infiltration 10 mm. or more in diameter was considered positive. Papulae of lesser diameter were recorded as negative. When the tuberculin study was finished, the person so tested, taking his registration card with him, had a photoroentgen examination made with equipment installed in his place of work.

A half-wave, self-rectified Siemens-Holdfelder portable apparatus was used, which was equipped with a specially designed 35 mm. Leica camera. At the time a picture was made, the number and name of the person examined was recorded photographically from the

registration card at the bottom of the film. Rolls of exposed film from these examinations were transported to the Institute for development and interpretation. Each film was projected and magnified to approximately 35 cm. on a screen and read simultaneously by at least two cooperating physicians.

Unsatisfactory or doubtful pictures were repeated. When pathologic changes were diagnosed in a small film, a standard-size roentgenogram was taken; special positions were employed if they appeared indicated. For these purposes, those suspected of having lesions came to the Institute of Phthisiology, where clinical and laboratory examinations which appeared necessary (hematologic, bacteriologic, et cetera) were made at the same time. The bacteriologic tests were carried out directly, by concentration and cultivation, on the sputum and also on gastric content or bronchial washings. Occasionally, animal inoculations were made.

Every person found to be ill was given rest treatment and medical care. Those of modest means were provided with hospital services; others were treated in their homes or in private sanatoriums. In all cases, however, the medical staff and inspectors of the institution maintained close periodic observation on the evolution of the disease, making sure that the sick persons followed the treatment instituted. This requirement is indispensable for beneficiaries of the National Terra Law of 1934, which guarantees to each tuberculous employee of the state uninterrupted leave of absence up to three years with full pay. Day laborers not permanently employed by the Government who are found to be tuberculous are also taken care of financially by the organization and simultaneously or later by the Honorary Commission for the Antituberculosis Campaign.

Photoroentgen examination has been carried out five times to date, viz., in the years 1940, 1947, 1948, 1949, and 1950. After 1947, because of the fact that in 1940 a positive tuberculin index of 97.6 per cent was encountered, the study of tuberculin sensitivity was abandoned. The writers were influenced in this decision by a desire to avoid all resistance on the part of the personnel to taking the examination, which the directorate of the organization established on a general basis and which it was possible to make mandatory.

In each annual investigation the personal clinical record of previous registrants was completed, with interrogation concerning recent incidents. New cases were registered in a corresponding manner. Every time that a person investigated reported an intercurrent disease suspected of tuberculous etiology, the Medical Office of the organization communicated the fact to the Institute, and sent the person concerned for examination at that time or as soon as possible.

Since 1947 all new employees, as a requisite for entrance into the organization, have come to the Institute to be examined. In 1947 the records were brought up to date on the 744 employees examined in 1940 by adding information on file in the medical office of the plants. In this way a record was made of those who had been sick with tuberculosis or who had been retired, or died from this disease.

OBSERVATIONS

Results Obtained in Five Systematic, Periodic Examinations in the State Electric and Telephone Plants up to 1950

In 1940, 851 persons were examined, but the present report is confined to results obtained in 744 who completed the tuberculin and photoroentgen investigation in accordance with the scheme outlined above.

Tuberculin tests: In table 1 the results of the tuberculin tests are summarized, classified by age groups. The sex is not distinguished because only 3 per cent of the total number were women.

As may be seen in table 1, 90.5 per cent of the persons tested showed a positive cutaneous reaction to the first test. The intradermic reaction with 1 mg. of tuberculin added 7.1 per cent to this value, giving a total of 97.6 per cent for persons

TABLE 1

RESULTS OF TUBERCULIN TESTS IN 744 PERSONS
(First Examination 1940)

AGE IN YEARS	NUMBER OF CASES			TOTAL PER CENT TUBERCULIN POSITIVE
	Total	Positive Cutaneous Reaction	Positive Intradermal Reaction (1 mg .OT)*	
11–15	3	3	0	100.0
16–20	31	24	2	83.9
21–25	108	95	10	97.2
26–30	141	136	4	99.3
31–35	134	123	9	98.5
36–40	116	108	7	99.1
41–45	61	58	4	98.8
46–50	80	70	8	97.5
51–55	41	35	4	95.1
56–60	23	17	5	95.7
61–65	4	4	0	100.0
66–70	2	2	0	100.0
Total	744 (100%)	673 (90.5%)	53 (7.1%)	97.6

* Old Tuberculin.

TABLE 2

COMPOSITION OF GROUP EXAMINED

STATUS	AGE IN YEARS	NUMBER OF CASES	NUMBER OF CASES TUBERCULIN POSITIVE
Training	11–20	34 (4.5%)	29
Productive	21–50	640 (86.1%)	630
Retired	50 and over	70 (9.4%)	67
Total		744 (100%)	726 (97.6%)

positive to tuberculin. Special attention should be paid to the high index of tuberculous infection encountered in this group, which was evident at an early age.

From the data in table 2, a general idea may be gained of the relative distribution of the three large groups, distinguished by economic and social character, which made up the sample examined. This distribution was maintained proportionately in the four examinations carried out later.

The limit of fifty-one years, recorded as the age of retirement, may seem too

low since it would be logical to set retirement at sixty-five years of age. The writers have attempted to be realistic in this respect, however, since a great majority of state employees, other than office chiefs or chiefs of subsidiaries, are entitled to retire when they have completed thirty years of service and have reached the age of fifty years. These stop work altogether or continue to work in a private activity free from regulations, while retired with full salary from the Pension and Retirement Office of the Public Services under the circumstances indicated.

Results of photoroentgen examinations: To avoid lengthy discussion on this phase of the work, the results of the five photoroentgen examinations are summarized and are limited to values for tuberculous lesions diagnosed as *active*. In this study, lesions were classified as *active* on the basis of their roentgenographic characteristics. Shadows of typical location, with ill-defined contours and the roentgenographic characters of exudative processes were considered as represent-

TABLE 3

TOTAL NUMBER OF PERSONS EXAMINED BY PHOTOROENTGENOGRAPHY IN FIVE INVESTIGATIONS (1940–1947)

YEAR	NUMBER EXAMINED AT EACH INVESTIGATION					TOTAL
	First	Second	Third	Fourth	Fifth	
1940	744					744
1947	4,849	660				5,509
1948	946	4,602	641			6,189
1949	564	396	4,071	593		5,624
1950	547	325	288	3,622	531	5,308
Total	7,650	5,983	5,000	4,215	531	23,374

ing active lesions. Confirmation was obtained through serial studies for evidence of progression or regression. Bacteriologic proof was secured in 75.5 per cent of the 86.7 per cent of cases in which examination for tubercle bacilli was possible.

The total number examined was 5,509 persons in 1947; 6,189 in 1948; 5,624 in 1949; and 5,308 in 1950. If to these are added the 744 persons seen in 1940, the total number examined in five successive investigations was 23,374. In table 3 the composition of each one of the groups examined each time is analyzed. In the first column of the table, the year in which the examination was carried out is designated. The second column records the number of persons examined for the first time in that year. The total is 7,650 persons separately registered and thus included in the study. In the third column appear those registrants who had a second serial systematic examination in the year of the corresponding horizontal line; these total 5,983 (78.2 per cent of the study sample). The fourth column records the 5,000 who had a third examination; in the last column is set forth the total number of persons examined in each one of the years designated in the first column of the table.

Between the first examination in 1940 and the second in 1947, seven years

transpired. If only those persons studied roentgenographically in four successive annual investigations (1947 to 1950) are included, the number of those examined totals 22,630. This total is made up as follows: 5,509 plus 6,189 plus 5,624 plus 5,308 = 22,630.

The number of person-years studied during these three annual periods was determined by the method of Frost, taking into account only those who were re-examined at least once. Of the 5,509 persons seen in 1947, 5,243 were re-examined in 1948 (4,602 studied for the first time in 1947 plus 641 of those investigated in 1940). Of the 946 persons examined for the first time in 1948, 396 were re-examined in 1949. Of the 5,243 re-examined in 1948, 4,664 underwent a third examination (4,071 plus 593 according to the method described above). The 396 added to the 4,664 makes a total of 5,060 additional person-years.

In 1950, 325 of the 564 persons first examined in 1949 were examined again, and 4,441 of the 5,060 examined in earlier years. The total number of person-years thus studied between 1947 and 1950 amounts to 15,069, calculated as follows: 5,243 plus 5,060 plus 4,766.

In the case of the 744 persons studied in 1940, the data filed in the individual record cards of each case in the medical office of the plant made it possible to establish the nature of those illnesses which compelled workers to request leave of absence while still employed, as well as the retirements and pensions granted for illness and the figures for deaths. In this way it was possible to discover who fell ill from tuberculosis.

Re-examination of 660 of these persons in 1947 brought to light the cases of latent tuberculosis then existing. It was also possible to discover residues of disease among those found normal at the time of the first examination who developed lesions which were never perceptible and were cured by spontaneous resolution.

In the seven years between 1940 and 1947, the person-years of observation of these 660 persons totaled 7 times 660, or 4,620. Thus, our conclusions are actually based on 19,689 tabulated person-years (4,620 plus 15,069).

The number of latent tuberculous processes encountered in the first examination of the 7,650 different persons composing the group studied is recorded in table 4. It was found that the prevalence of latent tuberculous lesions among the 7,650 persons seen for the first time in the five examinations was 1.07 per cent.

In the 660 employees seen in 1940 and for the second time in 1947, 6 cases of latent active tuberculosis, which are not recorded in table 4, appeared after the eight-year interim.

The incidence of latent tuberculosis, including cases detected in successive examinations in apparently healthy persons and cases in which residues of lesions were discovered in apparently normal persons in the examination immediately preceding, is specified in table 5.

In the line corresponding to the year 1947, the cases first observed in 1940 (641, 593, 531) and those seen for the first time in 1947 (4,602, 4,071, and 3,622) are indicated between parentheses for each re-examination for 1948, 1949, and 1950. This explanation is necessary since seven years, between 1940 and 1947, transpired without examinations. It is interesting to note that, although the

incidence found was low, a large proportion of the manifest processes which were discovered in the third annual examination did not represent new lesions in persons previously normal on roentgenographic examination. On the contrary, the manifest processes represented reactivations of residues of apparently cicatrized lesions which had been seen in previous examinations during a period of health. Actually, of 13 persons in whom active lesions were encountered in the third annual systematic examination, there were only 4 persons in whom the

TABLE 4

PREVALENCE OF LATENT ACTIVE TUBERCULOUS LESIONS IN THE GROUP STUDIED

YEAR	NUMBER EXAMINED FOR FIRST TIME	ACTIVE TUBERCULOSIS
1946	744	16
1947	4,849	55
1948	946	2
1949	564	1
1950	547	8
Total	7,650	82 (1.07%)

TABLE 5

INCIDENCE OF LATENT TUBERCULOUS PROCESSES FOUND IN FOUR SUCCESSIVE ANNUAL EXAMINATIONS

EXAMINED IN YEAR DESIGNATED		SECOND EXAMINATION ONE YEAR LATER		THIRD EXAMINATION TWO YEARS LATER		FOURTH EXAMINATION THREE YEARS LATER	
Year	Number	Number	Cases of Active Tuberculosis	Number	Cases of Active Tuberculosis	Number	Cases of Active Tuberculosis
1947	5,509	5,243 (641 + 4,602)	6	4,664 (593 + 4,071)	12	4,153 (531 + 3,622)	2
1948	946	396	1	288	1	—	—
1949	564	325	2	—	—	—	—
Total		5,964	9 (0.15%)	4,952	13 (0.26%)	4,153	2 (0.04%)

findings on previous examination were considered to have been normal. In the other 9 persons, a residue of some type had been diagnosed (calcification in 2 and significant sclerotic processes in the other 7), as indicated in detail in table 6.

As may be seen in table 6, of the 12 persons with active processes observed in the year 1949, 4 were roentgenographically normal in 1947 and 1948. Seven showed sclerotic processes in 1947 and 1948, and in one instance the examinations in those two years disclosed calcifications. In one case in which calcifications were detected in the first examination in 1948 and again in the second in 1949, an infiltration was revealed in the third examination in 1950.

When these 13 cases were reviewed in July, 1951, it was found that 4 of them remained active while 9 had become restabilized.

The incidence of latent lesions encountered in each one of the annual examina-

tions is recorded in table 6. During each period between investigations, however, a certain number of clinically manifest symptomatic processes appeared in persons who had been considered entirely healthy a few months previously.

TABLE 6

CASES OF ACTIVE TUBERCULOSIS FOUND IN THIRD ANNUAL ROUTINE EXAMINATION

NUMBER	YEAR AND RESULTS OF FIRST EXAMINATION		YEAR OF REACTIVATION		CLINICAL STATE IN 1951	
	1947	1948	1949	1950	Scarred	Active
4	Normal	Normal	Infiltration	—	4	—
1	Calcification	Calcification	Infiltration	—	—	1
4	Scar	Scar	Infiltration	—	4	—
1	Scar	Scar	Infiltration	—	—	1
2	Scar	Scar	Cavity	—	—	2
1	—	Calcification	Calcification	Infiltration	1	—
Total...13	12	1	12	1	9	4

TABLE 7

ANNUAL INCIDENCE OF MANIFEST TUBERCULOUS PROCESSES

FIRST YEAR OF OBSERVATION		PERSONS BECOMING ILL IN INTERVAL BETWEEN EXAMINATIONS				
		First to Second	Second to Third		Third to Fourth	
Year	Number of Cases	Cases of Manifest Tuberculosis	Total Examined	Manifest Tuberculosis	Total Examined	Manifest Tuberculosis
1947–1948	5,243	7 (0.13%)	4,664	0 (0%)	4,153	0 (0%)
1948–1949	396	3 (0.76%)	288	0 (0%)	—	—
1949–1950	325	7 (2.15%)	—	—	—	—
Total.....	5,964	17 (0.28%)	4,952	0 (0%)	4,153	0 (0%)

TABLE 8

ANNUAL INCIDENCE OF MANIFEST AND LATENT TUBERCULOSIS

EXAMINED IN YEAR	SECOND EXAMINATION		THIRD EXAMINATION		FOURTH EXAMINATION	
	Number of Cases	Active Tuberculosis	Number of Cases	Active Tuberculosis	Number of Cases	Active Tuberculosis
1947	5,243	13 (0.24%)	4,664	12 (0.25%)	4,153	2 (0.04%)
1948	396	4 (1.01%)	288	1 (0.34%)	—	—
1949	325	9 (2.76%)	—	—	—	—
Total.....	5,964	26 (0.43%)	4,952	13 (0.26%)	4,153	2 (0.04%)

The incidence of those manifest cases diagnosed between the routine annual examinations is recorded in table 7. It is seen that after the first examination, and actually during the first year following that examination, a number of manifest

cases (17 cases) appeared, which exceeded the number of latent cases (9 cases, table 5) encountered in the second annual investigation. No case of manifest tuberculosis appeared in the 641 persons investigated in 1948 who had been examined in 1940, corresponding to the 7 cases noted in the 4,602 persons actually seen for the first time in 1947.

Between the second and third examinations and between the latter and fourth examination, as in the group to which reference has just been made, no case of tuberculosis appeared. Thus, the annual incidence for each one of these periods included only the latent forms found in the routine photoroentgen examination. In table 8 is recorded the total number of cases of active tuberculosis, manifest or latent, diagnosed clinically or by routine annual photoroentgen examination in each twelve-month period of observation. The incidence of tuberculosis was 0.43 per cent in the first year, 0.26 per cent in the second, and 0.04 per cent in the third year of observation.

DISCUSSION

In the opinion of the writers, the sample chosen has permitted an investigation of almost experimental character for determining the prevalence and incidence of tuberculosis in a group of adults who were in the productive period of life in the majority of cases and composed almost exclusively of men. The proportion of women was 3.5 per cent in 1940, 6.75 per cent in 1947, 7.20 per cent in 1948, 7.69 per cent in 1949, and 7.98 per cent in 1950.

Because of the fact that most of the persons observed were government employees, it was possible to re-examine a large proportion of them routinely. In 7,650 different persons who had chest photoroentgen studies, it was possible to see 5,983 (77.9 per cent) for the second time a year later. In the third year, 5,000 were seen (83.6 per cent); and in the fourth year, 4,215 (84.3 per cent) of the 5,000 examined in the previous year. Of the 5,509 who were subjected to photoroentgen study in 1947, 5,243 were maintained under observation for at least one year, of whom 4,153 (79.2 per cent) were continued under observation in 1950. A large part of those not re-examined could not be followed because they had ceased working or had been retired or transferred to another division of the government. As has been indicated, a continuing medical supervision was maintained over the group by the facilities of the medical office of the organization.

In the opinion of the writers, the most important results of this investigation are the following three:

First, the results show that the Frost formula for person-years of examination is gravely at fault in ignoring, as here documented, the fact that the behavior of a human group, observed over a long time and composed of adults who were almost exclusively tuberculin positive at the beginning of the study, is completely different in the first and in the succeeding years in respect to incidence of manifest forms of tuberculosis. This is in spite of the fact that the formula is technically perfect as a means of obviating the difficulties of calculation incident to the variation in time during which the persons in the sample were under observation. The difference is explained by the fact that, among those examined in a first survey, there might have been a number who were infected for the first time recently.

The second significant finding is the progressive tendency, and therefore greater severity, of the clinically manifest forms of disease as compared with the latent forms encountered in routine examinations in healthy persons. At least this is true if the subjects are not subjected to massive contagion, as in the group included in the sample studied, which can be taken as representative socially of the population of Montevideo. The proof is the different and more severe clinical course of the disease and the necessity for more intense treatment required in the 17 persons with initial clinical onset as compared with the 9 latent cases.

TABLE 9

CASES WITH CLINICAL ONSET OR DIAGNOSED AS MANIFEST IN INTERVAL BETWEEN TWO EXAMINATIONS, AND STATUS IN 1951

ANNUAL INTERVAL	NUMBER OF CASES	TYPE OF LESION	STATUS IN 1951		
			Scarred	Active	Dead
1947–1948	6	Infiltration	4	—	1
	1	Tuberculous meningitis	—	—	2
1948–1949	1	Infiltration	1	—	—
1949–1950	5	Infiltration	2	3	—
	1	Cavity	—	1	—
Totals	14		7 (50.0%)	4 (28.6%)	3 (21.4%)

TABLE 10

LATENT LESIONS DIAGNOSED AT SECOND EXAMINATION AND STATUS IN 1951

YEAR OF SECOND EXAMINATION	NUMBER OF CASES	TYPE OF LESION	STATUS IN 1951		
			Scarred	Active	Dead
1948	5	Infiltration	5	—	—
1949	1	Cavity	1	—	—
1950	2	Infiltration	—	2	—
Totals	8		6 (75.0%)	2 (25.0%)	0

It is to be noted that, of the 17 clinically active cases which appeared in the interval between the two examinations, 14 were reviewed clinically, roentgenographically, and bacteriologically in 1951. Three day laborers who were not government employees had been discharged and therefore could not be followed. Of the remaining 14 whose cases could be reviewed, 7 (50 per cent) had inactive sclerotic processes, 3 (21.4 per cent) had died, and 4 (28.6 per cent) remained active (table 9).

A marked contrast is seen in the 9 latent cases diagnosed in a second examination at the end of the first year of observation, re-examined in 1948–1949 and 1950, and reviewed in 1951. One patient in this group died from cardiac failure in 1951. Of the remaining 8 patients, 6 (75 per cent) demonstrated inactive, and 2 (25 per cent) active, lesions. No one in this group had died from tuberculosis (table 10).

This different developmental tendency suggests that, in adults at least and probably also in younger persons, during the first or second year following tuberculous infection the human organism can demonstrate three types of reaction of roentgenographically

different aspect. Sometimes the phenomenon of allergy develops without roentgenographically visible localization or with nothing more than local adenopathy. In other cases, one or more discrete pulmonary foci are found at the time that allergy develops, with or without evident satellite lymph node reaction, which have little tendency to progress and remain latent. In such cases a state of symbiosis exists between the bacillus and the human organism, in which a pulmonary focus remains recognizable roentgenographically over a prolonged period.

The third important finding in the study is the occasional appearance of a pulmonary, pulmonary-lymph-node, or pleuropulmonary process of rapid progressive development, manifestly active almost from its start.

It is rather generally accepted that pulmonary tuberculosis ordinarily begins in a latent form. In the writers' opinion, in the light of the results of this study, latent tuberculosis is a sluggish and stable form which very rarely displays a tendency to progressive development and, therefore, is almost never the form of onset of chronic phthisis in persons with a good standard of living. This type of tuberculosis, asymptomatic, sluggish, and stationary, with but slight progressive tendency, might well be considered an expression of an excellent organic defensive state. It is found more frequently with advancing age in the group surveyed, as pointed out in previous articles by one of the present writers and confirmed in the first investigation carried out in the plant in 1940 where the distribution recorded in table 11 was encountered. As is evident, except for cases occurring before the age of twenty years in which recent first infections are presumably concerned, the percentage of latent active lesions increases steadily with age.

TABLE 11

LATENT ACTIVE TUBERCULOSIS

DISTRIBUTION BY AGE IN 16 CASES AMONG 744 PERSONS EXAMINED

AGE IN YEARS	PER CENT OF ACTIVE TUBERCULOSIS
11–20	5.0
21–30	0.8
31–40	1.6
41–50	3.3
51 and over	3.8
Average	2.1

If the findings recorded above are confirmed, the conclusion is logical that, if clinically manifest lesions do not appear in the two years immediately after the development of allergy, there is little probability that later rapidly developing forms of pulmonary tuberculosis will arise. In the majority of cases, latent lesions discovered would represent forms without a tendency to progressive development except under unfavorable conditions such as quantitative or qualitative malnutrition, as in wars or periods of crisis or famine. Undernourishment would favor temporary or permanent weakening of the organism, leading to a decline in the natural defensive powers and progressive activation of previously stationary and latent forms of the disease. This diminution of inherent resistance may also pave the way, in a transitory or prolonged manner, so that infections or

superinfections which would not cause recognizable lesions (state of maximal organic resistance) or, at the most, induce latent lesions (symbiosis characteristics of an intermediate defensive state) lead to a high incidence of pulmonary or lymph node lesions with marked progressive tendency. These in turn lead for a few years to more or less prolonged epidemics or waves of tuberculosis, with an increase of clinically manifest disease in acute disseminated, caseous, and extrapulmonary forms, as in the last two world wars or for a variable period of years in the industrial development of different countries.

This concept explains equally well the observation made by Edwards in the United States in 1940 (1) that Negroes, in spite of a tuberculosis mortality rate at least three times as high as that of white persons, show a lower incidence of latent lesions on routine roentgenographic examination. It also explains the apparently contradictory finding reported by Edwards and Drolet in the same country (2) that, while the tuberculosis mortality decreases, the morbidity as represented by latent disease increases.

The practical conclusion deduced from this exposition is that persons with latent disease, if kept under strict supervision and placed on a rest regimen, need not be hospitalized, at least in countries with an insufficient number of beds. Beds should be reserved for active treatment of clinically manifest tuberculosis in which the tendency is frequently progressive and destructive. In the worst of these cases, isolation diminishes the danger of contagion and dissemination.

SUMMARY

The results of routine annual photoroentgen examinations carried out during four consecutive years (1947–1950) on the personnel of the Electric and Telephone Plants of Uruguay are presented. The group was made up of office, shop, and outdoor workers. The mass examinations were supplemented by continuous medical supervision.

Of the group, 97.6 per cent were tuberculin positive. The total number of persons examined was 7,650. The prevalence of active tuberculous lesions found among them was 1.07 per cent (82 cases). The number of person-years of observation was 15,069. Of 5,507 persons studied in 1947, 79.2 per cent (4,153 cases) remained under observation in 1950. The incidence of latent tuberculosis detected roentgenographically at the end of the first year was 0.15 per cent; at the end of the second year, 0.26 per cent; and at the end of the third year, 0.04 per cent. There were 24 cases in all. The majority of such lesions were encountered in persons carrying the residues of previous disease.

In the course of the three years during which studies were made, 17 cases of manifest or symptomatic tuberculosis appeared between successive routine examinations. All of these developed between the first and second examinations of persons in the group studied. They accounted for 0.28 per cent of the persons followed during the three-year period. In the course of the second and the third years, no new case of tuberculosis with clinically manifest onset was discovered. The incidence of manifest and latent tuberculous cases combined was 0.43 per cent in the first year, 0.26 per cent in the second, and 0.04 in the third.

The latent forms were, in general, of mild course and regressive tendency. The clinically manifest and symptomatic cases showed a more frequent progressive tendency, resulting in fatality in 21.4 per cent of cases.

These results lead to the conclusion that latent tuberculosis discovered by roentgenographic examination of apparently healthy persons rarely represents the onset of progressive phthisis in the adult. It is usually a benign form of pulmonary tuberculosis in persons with good inherent resistance.

SUMARIO

La Incidencia de la Tuberculosis Pulmonar en un Grupo Observado Continuamente y Reexaminado Periódicamente

Se presentan los resultados del examen roentgenfotográfico sistemático anual realizado durante cuatro años seguidos (1947–1950) entre el personal de las Usinas Eléctricas y de Teléfonos del Uruguay integrado por oficinistas, obreros de talleres y otros con trabajo a la intemperie.

Los resultados de estos exámenes en masa se complementaron con vigilancia médica permanente de las personas estudiadas.

El 97.6 por ciento resultó tuberculinopositivas. El número total de personas examinadas fué 7,650 y la prevalencia de lesiones tuberculosas activas en ellas de 1.07 por ciento (82 casos).

El número de personas-año vigiladas alcanzó a 15,069. De las 5,507 estudiados en 1947 continuaban bajo vigilancia en 1950 el 79.2 por ciento (4,153 casos).

La incidencia tuberculosa inaparente encontrada radiológicamente al final del primer año fué de 0.15 por ciento; de 0.26 por ciento al segundo; y de 0.04 por ciento al terminar el tercero. En total sumaron 24 casos. Buena proporción de los mismos se presentó en portadores de estados secuela.

En el correr de los tres años encarados aparecieron entre uno y otro examen sistemático anual, otros 17 casos de tuberculosis aparente o sintomática, todos ellos en el curso del primer año, lo que dió un 0.28 por ciento de procesos aparentes en el primer año de observación. En el transcurso del segundo y del tercer año no se presentó ningún nuevo caso de tuberculosis con iniciación clínica aparente.

La incidencia de procesos tuberculosos aparentes e inaparentes fué de 0.43 por ciento en el primer año; de 0.26 por ciento en el segundo y de 0.04 por ciento en el tercero.

Los procesos inaparentes fueron en general de evolución lenta y fácil tentencia regresiva. Los clínicamente aparentes o sintomáticos, mostraron mayor tendencia evolutiva y progresiva, resultando mortales en un 21.4 por ciento.

Estas comprobaciones llevan a concluir que la tuberculosis inaparente descubierta por examen radiológico del aparentemente sano en pocos casos representa el comienzo de la tisis consuntiva del adulto. Sería una forma benigna de tuberculosis pulmonar observable en personas con buenas defensas orgánicas.

RESUME

Incidence de la tuberculose pulmonaire dans un groupe soumis à l'observation continue et réexaminé périodiquement

Présentation des résultats d'examens radiologiques annuels systématiques avec radiogrammes, effectués pendant quatre années consécutives (1947–1950) chez le personnel de la compagnie "Electric & Telephone Plants de l'Uruguay". Le groupe comprenait le personnel des bureaux et les ouvriers des ateliers et de l'extérieur. Les examens collectifs étaient complétés par une surveillance médicale continue.

Dans ce groupe, 97,6% des sujets avaient un tuberculin-test positif. Le nombre total d'individus examinés était de 7.650. La proportion de lésions tuberculeuses en activité

découvertes parmi eux était de 1,07% (82 cas). Le nombre homme-années d'observation était 15.069. Parmi les 5.507 personnes étudiées en 1947, 79,2% (4.153 cas) demeuraient en observation en 1950. L'prevalence de la tuberculose latente dépistée radiologiquement était, à la fin de la première année, de 0,15%; à la fin de la deuxième année de 0,26%; à la fin de la troisième année de 0,04%. Le nombre total des cas était de 24. La majorité de ces lésions étaient rencontrées chez des individus qui conservaient des séquelles d'une affection antérieure.

Au cours des trois années de la durée de ces études, 17 cas de tuberculose manifeste ou symptomatique se sont révélés entre les examens périodiques successifs. Chez les sujets du groupe étudié, tous ces cas se sont développés entre la première et la seconde série d'examens. Ces cas représentaient 0,28% des individus observés pendant cette période de trois ans. Au cours de la deuxième et de la troisième année il n'a été découvert aucun cas nouveau de tuberculose avec début clinique manifeste. En tout, l'incidence des cas de tuberculose manifeste ou latente réunis était de 0,43% dans la première année, 0,26% dans la deuxième année et 0,04% dans la troisième.

Les formes latentes avaient en général un cours modéré et une tendance à la régression. Les cas cliniquement manifestes et symptomatiques présentaient plus fréquemment une tendance à la progression, leur taux de mortalité était de 21,4%.

Ces résultats amènent à conclure que la tuberculose latente, décelée par l'examen radiologique chez des individus paraissant bien portants, constitue rarement, chez l'adulte, le début d'une tuberculose pulmonaire évolutive. Il s'agit habituellement de la forme bénigne de tuberculose pulmonaire observée chez des sujets disposant d'une résistance innée satisfaisante.

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INCIDENCE OF PULMONARY TUBERCULOSIS AMONG EMPLOYEES OF TUBERCULOSIS HOSPITALS[1]

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INTRODUCTION

One of the most common questions in tuberculosis control is whether persons working in tuberculosis hospitals have a higher risk of developing tuberculosis than persons in comparable age groups who are employed in other environments. The fairly extensive literature on this general subject has been well summarized and brought up to date in the publication *Tuberculosis Among Hospital Personnel* by E. C. Connolly (1).

Much of the past work has been concerned with the risk of developing tuberculous *infection*. Nevertheless, as Connolly notes: "in the final analysis, tuberculosis as an occupational hazard among hospital personnel must be measured in terms of active disease suffered by these persons and not by the amount of tuberculous infection incurred by them." She further states that morbidity among the hospital and the non-hospital groups can be properly evaluated and compared "only after an investigation of a sufficient number of persons within each group drawn originally from the same background. The groups must then be followed for a period of time long enough to establish significant results."

Despite the fact that a large number of studies have been reported, two main difficulties have made impossible the formulation of any definite conclusions. One is that many of the studies have not included true annual incidence or attack rates, but have merely stated the total incidence which has occurred over a certain period of years, usually expressed as a percentage. The second main problem has been the lack of data regarding incidence of tuberculosis in the general population, that is, data for the non-hospital groups of employed persons with which to compare findings among hospital personnel.

In regard to the last-named point, it might be presumed that the extensive mass chest roentgenographic survey programs conducted in recent years might have provided opportunities to study incidence of tuberculosis among persons examined more than once at intervals of time. To be sure, a few such studies have been done, usually in selected groups of the population. Nevertheless, most agencies which have organized large-scale mass chest roentgenographic survey programs have deliberately decided not to plan for studies of incidence through

[1] From the New York State Department of Health, Albany, New York; the Homer Folks Tuberculosis Hospital, Oneonta, New York; the Hermann M. Biggs Memorial Hospital, Ithaca, New York; and the Mount Morris Tuberculosis Hospital, Mount Morris, New York.

retention of records and comparison of films taken initially and upon resurvey of specifically identified persons. This is because of the tremendous practical procedural problem which such an undertaking would involve in so far as records, roentgenograms, and files are concerned. Moreover, a much greater immediate need and objective of this aspect of tuberculosis control is to obtain roentgenographic examinations even once on as many adults of the population as quickly and cheaply as possible.

Most of the reported studies on tuberculosis in hospital personnel have indicated that the incidence of tuberculosis among nurses in general hospitals and in tuberculosis hospitals is higher than the incidence in comparable age and sex groups in the general population. Moreover, the risk appears to be higher in tuberculin nonreactors than in reactors. Nevertheless, very few comprehensive studies of tuberculosis among *all* groups of tuberculosis hospital employees have been reported. Connolly (1) summarizes the findings in three such studies as follows:

> The study made at Manitoba Sanatorium is a comprehensive one, covering the total staff employed at this institution in the years 1938 to 1943, inclusive. Twelve cases of tuberculosis developed among 559 persons, the majority of whom were female. The annual incidence rate was 1.4 per cent according to computation by modified life table. [When those with previously known tuberculosis are removed from the experience, the rate is 1.8 per cent per year.]
>
> Not one of the twelve patients was a nurse. Eight were attendants, which meant that two-thirds of the patients came from this group. Upon arrival attendants showed a much lower rate of infection than nurses since they were younger, were mainly from rural areas, and had experienced little previous exposure to tuberculosis.
>
> Two English tuberculosis hospitals have published studies of tuberculosis among staff personnel. King George V Sanatorium had an annual incidence of only 0.7 per cent among 2,009 persons joining the staff during a twenty-five-year period. Among the staff were 510 student nurses who remained for an average period of three months.
>
> At Cheshire Joint Sanatorium, over a period of seven years, ten cases of tuberculosis developed among 48 employees, an incidence of 45 per 1,000 observation years, but all cases were primary tuberculosis which proved not to be progressive.

Connolly refers also to a study by Childress at Grasslands Hospital, Westchester County, New York. In a more recent paper, Childress (2) reports the findings in a longer period (1932 to 1950). Grasslands is a general hospital with a separate tuberculosis service. Most important was the finding that, among employees exposed to tuberculosis patients, the attack rate was 6.6 per 1,000 person-years while among those without such exposure the rate was only 1.3 per 1,000 person-years. The rate among the exposed was thus five times higher than among the nonexposed.

Still another type of hospital group was recently studied by Katz, Plunkett, and MacCurdy (3) as part of a comprehensive tuberculosis control program con-

ducted by the New York State Department of Health in the institutions for the mentally ill operated by the State Department of Mental Hygiene. A study of the incidence of tuberculosis among employees of fourteen of these institutions showed that new cases developed at a rate of 7.81 per 1,000 person-years in those employed on the tuberculosis wards as compared with a rate of 0.72 in those employed on other wards; the former rate is thus ten times as high as the latter.

Regardless of the type of hospital under consideration, this subject obviously has significant implications with respect to such important administrative matters as recruitment of personnel, affiliation programs for student nurses and others, extra compensation for employees because of hazardous employment, and Workmen's Compensation.

The present study was made possible through the establishment of a program of routine periodic examination of employees of the three New York State tuberculosis hospitals which were opened in 1935 and 1936 at Oneonta, Mount Morris, and Ithaca, New York. The purpose of the study was to determine the comparative incidence of tuberculosis among various groups of employees in these hospitals and thus the relative hazard of exposure to tuberculosis in the various services.

MATERIAL AND METHOD

The sources of information were the employees' medical records at the hospitals. Comprehensive inclusion of all persons who had ever worked at the hospitals was assured by primary reference to the master index file of employees maintained in the business offices. The beginning date of the study coincided with the dates of opening of the three hospitals, the earliest being December, 1935. The observation period was terminated on December 31, 1948. The capacity of each of these hospitals is 250 beds; during the period of the study, the approximate average number of employees in each hospital was slightly more than 200.

The following items of information from the employees' medical records were abstracted:

Employee's initials: If an employee had been employed two or more different times, he was counted only once and the various periods of employment were added. For persons out on leave of absence, the total numbers of months actually at work were similarly added.

Sex.

Age at the time of employment.

Occupational group: Persons were classified in the service in which they had worked one-half or more of the total period from the time first employed to the end of the observation.

Year employed.

Result of tuberculin test at time of first employment.

Presence or absence of tuberculosis at time of employment.

Number of months observed: This corresponded to the number of months employed. The end of observation was any one of the following conditions:

a. Diagnosis of definite tuberculosis
b. Discontinuation of employment
c. Neither (a) nor (b), and still working as of December 31, 1948, the end of the study period

Diagnosis at end of observation.

The analysis included a count of the employees with tuberculosis at the time of employment and computation of annual attack or incidence rates of tuberculosis according to age, sex, occupational service, and status of tuberculin reaction at the time of employment. A modified life-table method was used, and the rates were computed on the basis of the number of person-years of observation.

No attempt was made to analyze the subsequent course and outcome of the new cases which developed during the period of observation. Other studies have shown quite uniformly, however, that, because of early diagnosis and early treatment under circumstances such as these, there is a low fatality rate and, in general, an outcome which is much better than among tuberculosis cases generally.

RESULTS

The total number of persons employed during the period of the study was 3,492. There were 384 persons (11 per cent) with a diagnosis of tuberculosis at the time of employment and they were properly excluded from the incidence study; 371 of these 384 persons had healed pulmonary tuberculosis, 8 had nonpulmonary tuberculosis, and 5 had active pulmonary tuberculosis.

TABLE 1

TOTAL INCIDENCE OF TUBERCULOSIS CASES, BY SEX

SEX	NUMBER OF EMPLOYEES	PERSON-YEARS OF OBSERVATION	NUMBER OF CASES	RATE PER 1,000 PERSON-YEARS
Total	2,664	5,583.3	51	9.1
Male	968	2,291.4	17	7.4
Female	1,696	3,291.9	34	10.3

Another 444 persons, or 13 per cent of the total, were excluded from the incidence study because they were employed less than one month, this period having been arbitrarily selected as a minimum warranting consideration with respect to risk of developing tuberculosis.

The total number excluded from the original 3,492 was thus 828, leaving a balance of *2,664* persons who had no evidence of tuberculosis at the time of employment and who were employed more than one month and who thus constitute the group included in the study of incidence.

Total incidence: The minimum period of observation of the 2,664 employees was one month and the maximum was 157 months. The total number of person-years of observation was 5,583.3; a total of 51 cases of pulmonary tuberculosis developed among the 2,664 employees, representing a rate of 9.1 cases per 1,000 person-years (table 1).

Among the 968 males were 17 cases, a rate of 7.4 per 1,000 person-years; and among 1,696 females were 34 cases, a rate of 10.3. This difference between the rates for the two sexes is not statistically significant.[2]

[2] The total incidence rate per 100 persons employed was 1.9, with a rate of 1.8 for males and 2.0 for females. This difference is also not statistically significant. Furthermore, standardization of the rates for the age distribution in each sex group results in similar rates, namely, 9.0 per 1,000 person-years for males and 9.3 for females.

Age and sex: As compared with the total incidence rate of 9.1 per 1,000 person-years, the rate was highest (23.4) in those less than 25 years of age, and then decreased with age (table 2). The age-specific rates showed these same characteristics in each of the two sex groups.

TABLE 2

INCIDENCE OF TUBERCULOSIS CASES BY SEX AND AGE AT TIME OF EMPLOYMENT

AGE AT TIME OF EMPLOYMENT	NUMBER OF EMPLOYEES	PERSON-YEARS OF OBSERVATION	NUMBER OF CASES	RATE PER 1,000 PERSON-YEARS
Both sexes				
Total	2,664	5,583.3	51	9.1
Under 25	856	1,112.5	26	23.4
25–34	784	1,878.6	18	9.6
35–44	425	1,203.6	3	2.5
45 or over	533	1,274.3	4	3.1
Not stated	66	114.3	—	—
Male				
Total	968	2,291.4	17	7.4
Under 25	237	303.0	6	19.8
25–34	298	774.6	8	10.3
35–44	145	405.8	1	2.5
45 or over	252	734.3	2	2.7
Not stated	36	73.7	—	—
Female				
Total	1,696	3,291.9	34	10.3
Under 25	619	809.5	20	24.7
25–34	486	1,104.0	10	9.1
35–44	280	797.8	2	2.5
45 or over	281	540.0	2	3.7
Not stated	30	40.6	—	—

Occupational group: Some 70 position titles in the hospitals were first classified into 12 occupational groups and for purposes of tabulation and analysis these were further reduced to the following seven groups (table 3):

Medical—Physicians and dentists

Nursing—Nurses and nursing attendants (Affiliate student nurses were excluded from this study.)

Technical—Bacteriologists, laboratory technicians, X-ray technicians, dental hygienists, teachers, medical social workers, occupational therapists, pharmacists

Dietary: Ward service—Dietitians, dining room attendants

Laundry—Laundry supervisors and launderers

Housekeeping—Housekeepers, domestics (maids), cleaners

Other—Dietary employees engaged in food preparation (bakers, cooks, kitchen helpers, meat cutters), all business office employees, stenographers, clerks, maintenance employees

The rate was highest (20.9) in the nursing group, in which 27 of the total 51 cases occurred. In male nurses the rate of 52.1 was far in excess of that in any other group; it was also considerably higher than the rate of 16.7 in female nurses, this difference being statistically significant.

TABLE 3

INCIDENCE OF TUBERCULOSIS CASES BY OCCUPATIONAL GROUP AND SEX

OCCUPATIONAL GROUP	NUMBER OF EMPLOYEES	PERSON-YEARS OF OBSERVATION	NUMBER OF CASES	RATE PER 1,000 PERSON-YEARS
Both sexes				
Total	2,664	5,583.3	51	9.1
Medical	60	128.3	1	7.8
Nursing	680	1,290.1	27	20.9
Technical	102	243.9	3	12.3
Dietary: ward service	601	756.6	8	10.6
Laundry	125	345.0	3	8.7
Housekeeping	376	807.5	6	7.4
Other	720	2,011.9	3	1.5
Male				
Total	968	2,291.4	17	7.4
Medical	57	118.6	1	8.4
Nursing	105	153.5	8	52.1
Technical	43	110.7	3	27.1
Dietary: ward service	70	60.6	—	—
Laundry	29	101.4	—	—
Housekeeping	128	250.7	3	12.0
Other	536	1,495.9	2	1.3
Female				
Total	1,696	3,291.9	34	10.3
Medical	3	9.7	—	—
Nursing	575	1,136.6	19	16.7
Technical	59	133.2	—	—
Dietary: ward service	531	696.0	8	11.5
Laundry	96	243.6	3	12.3
Housekeeping	248	556.8	3	5.4
Other	184	516.0	1	1.9

Of special interest is the fact that all 3 cases in the "technical" group occurred among 18 male laboratory employees.

Study of the rates in the various occupational groups according to age shows that in the nursing group the rates are highest in each sex group in those less than 25 years of age. In general, the numbers of cases in the individual age, sex, and occupational groups were too small to warrant detailed analysis.

The medical, nursing, technical, ward service dietary, laundry, and housekeeping groups represent employees who, through usually working with patients

or in other ways, may have direct opportunity for exposure to tubercle bacilli. In table 3A the rate for these "exposed" occupations is compared with that for all "other" occupations, those who do not usually or directly have the risk of such exposure. The rate of 13.4 in the "exposed" occupations is nine times as high as the rate of 1.5 in the other or "nonexposed" occupations.

TABLE 3A

INCIDENCE OF TUBERCULOSIS CASES BY OCCUPATIONAL GROUP

OCCUPATIONAL GROUP	NUMBER OF EMPLOYEES	PERSON-YEARS OF OBSERVATION	NUMBER OF CASES	RATE PER 1,000 PERSON-YEARS
Total	2,664	5,583.3	51	9.1
"Exposed"	1,944	3,571.4	48	13.4
Other ("Nonexposed")	720	2,011.9	3	1.5

TABLE 4

INCIDENCE OF TUBERCULOSIS CASES BY TUBERCULIN STATUS AT EMPLOYMENT AND SEX

TUBERCULIN STATUS AT EMPLOYMENT	NUMBER OF EMPLOYEES	PERSON-YEARS OF OBSERVATION	NUMBER OF CASES	RATE PER 1,000 PERSON-YEARS
Both sexes				
Total	2,664	5,583.3	51	9.1
Positive	1,302	2,498.1	23	9.2
Negative	789	1,278.5	22	17.2
Not tested	573	1,806.7	6	3.3
Male				
Total	968	2,291.4	17	7.4
Positive	486	974.1	6	6.2
Negative	236	396.1	6	15.1
Not tested	246	921.2	5	5.4
Female				
Total	1,696	3,291.9	34	10.3
Positive	816	1,524.0	17	11.2
Negative	553	882.4	16	18.1
Not tested	327	885.5	1	1.1

Status of cutaneous tuberculin reaction at time of employment: Of 2,091 employees who were tuberculin tested at the time of employment, 1,302 (62 per cent) were reactors[3] and 789 (38 per cent) were nonreactors (table 4). The incidence rate of 17.2 among the nonreactors was almost twice the rate of 9.2 among reactors;

[3] All but a small number of employees were tested with an initial dose of 0.0002 mg. of purified protein derivative (PPD) intracutaneously, and nonreactors to this dose were retested with 0.005 mg. of PPD.

the difference was higher among males (15.1 and 6.2, respectively) than among females (18.1 and 11.2, respectively).

The number of cases and the rates among reactors and nonreactors in the various age groups, both sexes, is shown in table 5.

In those less than 25 years of age, the rate of 35.8 among nonreactors is approximately twice as high as the rate of 18.8 among reactors. But in the next age group of 25 to 34 years, the situation is just the reverse, with a rate of 15.5 among reactors and 7.7 among nonreactors.

It may be reasoned that, if nonreactors have a *truly* higher incidence rate than reactors, this should be so in *all* age groups. As this was not so, however, it seemed

TABLE 5

INCIDENCE OF TUBERCULOSIS CASES BY TUBERCULIN STATUS AT EMPLOYMENT AND AGE

AGE	REACTORS		NONREACTORS	
	Cases	Rate	Cases	Rate
Total	23	9.2	22	17.2
Under 25	8	18.8	16	35.8
25–34	12	15.5	3	7.7
35–44	2	3.4	1	4.7
45 or over	1	1.5	2	10.6

TABLE 6

CRUDE AND STANDARDIZED INCIDENCE RATES BY TUBERCULIN STATUS AT EMPLOYMENT AND SEX

SEX	REACTORS		NONREACTORS	
	Crude	Standardized	Crude	Standardized
Both sexes	9.2	10.5	17.2	14.4
Male	6.2	6.5	15.1	13.0
Female	11.2	12.7	18.1	15.2

advisable to correct for differences in age composition of the two groups by standardizing the rates for age. The comparison of the crude and the standardized rates in the two sexes is shown in table 6. Standardization considerably reduces the size of the difference in the rates among reactors and nonreactors; for example, whereas the crude rates for both sexes are 9.2 among reactors and 17.2 among nonreactors, the standardized rates are 10.5 and 14.4, respectively.

Higher incidence rates in nonreactors have been found in most of the other studies reported. The reversal in the 25 to 34 age group may be due to the relatively small numbers involved in some of the groupings. Also, small numbers make unwise the search for possible other explanations in terms of occupational service, length of employment, and other factors. Sixteen of the 23 cases among reactors and 8 of the 22 cases among nonreactors were in nurses.

DISCUSSION

The primary question under consideration is the *relative* risk of developing tuberculosis for persons employed in tuberculosis hospitals. The results of this study can be related to this question from two standpoints.

First, one can attempt a comparison of the total incidence of new cases of tuberculosis among these tuberculosis hospital employees with the incidence in the general population. As stated in the introduction, there is unfortunately little, if any, representative information about the latter. A "kind" of incidence can be derived, however, from the number of new cases of tuberculosis reported annually. This was done in the report of Katz, Plunkett, and MacCurdy (3), who state that "while the cases reported in any given year do not necessarily represent those that develop during that year, nevertheless, over a period of time, the number reported may be considered an approximation of the rate of development of new cases." Based on the newly reported cases for New York State, exclusive of New York City, for a period of several years, the estimated rate is 1.00 new case per 1,000 population 15 years of age or older per year; the rate is approximately the same in the various age groups over 15.

The incidence rate among all employees in this study of 9.1 per 1,000 person-years is thus *nine* times as high as that estimated rate in the general population. Lim-Yuen (4) reported a rate of 18.0 among all employees of the Manitoba Tuberculosis Sanatorium.

Comparing the rates in just the "exposed" occupational groups with the estimated rate of 1.00 in the general population, in the present study that rate was 13.4. Childress (2) found a rate of 6.6 among exposed employees in a general hospital, and Katz (3) a rate of 7.81 in mental institutions among employees working on tuberculosis wards.

It is recognized that the estimated rate in the general population is a very crude estimate. Moreover, the conditions of comparison between the general population and the group under study are different, since in one the cases are counted only if they have been reported; while in the latter all cases occurring in the observed group are counted. The absolute figures for the two groups do not matter, however; the only point is that the observed rate in the present study group appears to be considerably higher than the probable true rate in the general population, even though the latter may be two or three or even more times as high as the estimate used for comparison.

The second approach to the question of relative risk is through comparison of incidence rates among the exposed and the nonexposed employees in the three different types of hospitals represented in these studies:

	Exposed	*Nonexposed*	*Ratio*
Present study	13.4	1.5	9:1
Childress (2)	6.6	1.3	5:1
Katz, Plunkett, and MacCurdy (3)	7.81	0.72	11:1

All of the 12 cases in the Manitoba study were in the "maximal and moderate exposure" groups (8 "attendants", 2 cleaners, and 2 diet kitchen maids).

There may be factors which influence the comparability of these studies, and the fact that a person develops tuberculosis after exposure to it in a hospital is not conclusive evidence of causal relationship. Nevertheless, the extent of the difference in the rates among those exposed and those not usually exposed is such as to suggest strongly that working in areas where exposure to tubercle bacilli is apt to occur is accompanied by a significantly greater risk of developing tuberculosis than otherwise.

As for the other findings in this study, there was no difference in the incidence rates among males and among females. Secondly, in both sexes the highest rates were in employees less than 25 years of age. In the absence of factual data on incidence in the general population, the significance of these findings is not known.

In terms of successive six-month periods during the first two years of employment, there seemed to be no definite association between the duration of employment and the development of tuberculosis; however, the incidence rates were considerably higher in the first two years of employment than after the second year.

The variation in rates in the various occupational groups is of considerable interest and importance. Of the total 51 new cases, 27, or more than half, were in the nursing group. This finding corroborates the results of the many studies among nurses, which have demonstrated the relatively high hazard in this occupation. The present study also shows, however, that there is a substantial hazard to workers in the technical, ward dietary, laundry, and housekeeping groups (table 3).

The finding of a higher incidence rate among nonreactors than among reactors to tuberculin corresponds to the results of most of the previous studies, particularly those of nurses. An interesting sidelight of this study is that, when these rates are standardized to adjust for differences in the age composition of reactors and nonreactors, the size of the difference in rates becomes considerably smaller. Of additional interest in this connection is the report of Badger and Ayvazian (5) which shows that in a *long-term* observation of five to fifteen years there was no difference in the number of cases of tuberculosis developing among nurses who were initially nonreactors and reactors to tuberculin.

Some years ago the belief existed that employees of tuberculosis hospitals did not develop tuberculosis with any undue frequency. It may be that the favorable experience enjoyed by many of the older sanatoriums through the years was due to the fact that in these institutions where both patients and employees were tuberculosis conscious, the effective transmission of the disease was materially reduced. Many other, and perhaps equally important, factors may have been contributory, however, such as the age of the employees, the duration of exposure, and the inability to determine exactly the source of the infection. Of probably the greatest importance is the fact that the observations were made before the value of serial chest roentgenograms in detecting early or subclinical infiltrations had come to be generally appreciated and before systematic case-finding programs among the employees were inaugurated.

In the three hospitals concerned in the present study, the relatively high attack rate of new cases occurred despite the existence of a constant awareness of the hazard and also of a planned program of training in, and application of, infectious disease techniques. In this connection, it is important that 36 of the total 51 cases developed among persons first employed during the first five years of operation of the hospitals. Moreover, the number of cases has progressively decreased. Nevertheless, the findings certainly indicate the need for constant, rigid application of preventive techniques and measures. BCG vaccination was begun only at approximately the time this study was terminated, so that its effectiveness in reducing morbidity in this group has yet to be determined.

SUMMARY

Among 2,664 employees of three state tuberculosis hospitals observed for periods ranging from one month to 157 months, 51 new cases of pulmonary tuberculosis developed, an incidence rate of 9.1 cases per 1,000 person-years. This rate is nine times as high as the estimated rate in the general population.

The rate among employees working in "exposed" occupations was 13.4 cases per 1,000 person-years, or nine times as high as the rate of 1.5 among those in "nonexposed" occupations.

The incidence rate was highest in the nursing group (20.9), but the rates were also high for employees in the technical (12.3), ward dietary (10.6), laundry (8.7), and housekeeping (7.4) groups.

The age-standardized rate among those who were nonreactors to tuberculin at the beginning of employment was 14.4 as compared with a rate of 10.5 among reactors.

The study demonstrates that employees in tuberculosis hospitals appear to have a substantially high risk of developing tuberculosis. As a consequence, constant and rigid preventive measures must be maintained in order to reduce the hazard to a minimum.

SUMARIO

Incidencia de la Tuberculosis Pulmonar entre los Empleados de los Hospitales para Tuberculosos

Entre 2,664 empleados de tres hospitales estatales de tuberculosis, observados durante períodos de tiempo que variaron de un mes a 157 meses, aparecieron 51 casos nuevos de tuberculosis, o sea un índice de incidencia de 9.1 casos por 1,000 años-personas. Esa tasa es nueve veces tan alta como la calculada para la población general.

El coeficiente entre los empleados dedicados a ocupaciones "expuestas" fué de 13.4 casos por 1,000 años-personas, o nueve veces tan alto como el 1.3 observado entre los empleados en ocupaciones "inexpuestas."

La incidencia alcanzó su máximo en el grupo de enfermeras, pero los coeficientes fueron también altos en los grupos técnico (12.3), dietético de sala (10.6), de lavandería (8.7) y de domésticos (7.4).

El coeficiente, uniformizado en cuanto a edad, entre los que no reaccionaron a la tuberculina al comenzar su empleo fué de 14.4, comparado con 10.5 entre los reactores.

Este estudio demuestra que los empleados de los hospitales para tuberculosos parecen correr un riesgo decididamente alto de contraer tuberculosis y que, por lo tanto, a fin de reducir el peligro al mínimo, hay que aplicar constantes y rígidas medidas preventivas.

RESUME

Incidence de la tuberculose pulmonaire parmi le personnel des hôpitaux pour tuberculeux

Parmi les 2.664 employés de trois hôpitaux d'Etat, réservés à la la tuberculose, qui ont été soumis à la surveillance médicale pendant des périodes s'échelonnant de 1 à 157 mois, 51 nouveaux case de tuberculose pulmonaire se sont produits; le taux de fréquence étant de 9,1 cas par 1.000 homme-années. Ce taux est neuf fois plus élevé que le taux établi pour la population générale.

Le taux, pour le personnel travaillant dans des conditions "d'exposition" était de 13,4 cas par 1.000 homme-années, c'est à dire neuf fois plus élevé que le taux de 1,5 pour le personnel "non exposé".

Le taux de fréquence le plus élevé était celui du groupe du personnel infirmier (20,9) ce taux était également élevé chez les techniciens (12,3), les diététiciens de salles (10,6) les blanchisseurs (8,7) et le personnel auxiliaire (7,4).

Le taux par groupe d'âge, pour les sujets anergiques à la tuberculine au début de leur entrée en fonction était de 14,4, par comparaison avec le taux de 10,5 obtenu pour les sujets allerigiques.

Cette étude démontre que le *risque de* développement de la tuberculose dans le personnel des services de la tuberculose est important et que des mesures de prévention, constantes et rigides, doivent être mises en oeuvre de manière à réduire au minimum le risque d'infection.

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LIPIDS OF LIVING AND KILLED TUBERCLE BACILLI[1, 2]

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INTRODUCTION

Anderson and his collaborators have carried out extensive work on the composition of the lipids of the tubercle bacillus. (For a review of the literature see Anderson (1, 2).) He subjected live bacilli to prolonged extraction with chloroform. The extracts were fractionated according to solubility in various solvent mixtures. The main fractions which he describes are acetone-soluble fat from the alcohol-ether extract, a phosphatide precipitated from ether by acetone, and a wax from the ether-acetone mother liquor. The chloroform extracts contained a crude wax which was separated into a soft wax and a "purified" wax. The latter was split on hydrolysis to give a polysaccharide and "unsaponifiable" wax. Asselineau and Lederer (4) showed that the salts of mycolic acid were soluble in ether and that, in fact, the "purified wax" was an ester of polysaccharide with mycolic acid, while the "unsaponifiable" wax was free mycolic acid. Anderson found that this "unsaponifiable wax" was the only acid-fast component to be isolated.

Choucroun (6) extracted autoclaved bacilli with paraffin oil and found a lipo-polysaccharide which was acid fast.

Asselineau and Lederer (4) made a study of acid-fastness in extracts of tubercle bacilli made by Anderson's method. After precipitation by acetone or methyl alcohol, they extracted the precipitate with boiling acetone and fractionated the extract by chromatography on neutralized alumina. The hot acetone extract from both the initial extracts with alcohol-ether and with chloroform revealed two components: a neutral substance, not acid fast, melting at 28° to 33°C., and free mycolic acid, melting at 53° to 57°C. Anderson's phosphatide and Choucroun's lipo-polysaccharide were insoluble in boiling acetone. Asselineau (3) further showed that Choucroun's lipo-polysaccharide was an ester of mycolic acid.

Bloch (5) extracted live tubercle bacilli with petroleum-ether, leaving the bacilli still viable. The alcohol precipitate of this extract he called "cord factor" and claimed certain biologic properties for it, such as inhibition of leukocyte migration and toxicity in certain strains of mice. He further stated that the "factor" could only be extracted from living virulent bacilli and that only those extracts which contained the factor stained solidly acid fast.

The work to be described in the present report began as a study of petroleum-ether extracts of live and heat-killed bacilli, and was extended to a comparison of extracts of live and heat-killed bacilli, using other solvents.

[1] From the Sir William Dunn School of Pathology, Oxford, England.

[2] Aided by grants from the Agricultural Research Council and the Medical Research Council.

EXPERIMENTAL

Production of Tubercle Bacilli

Live bacilli. Virulent tubercle bacilli of human type were grown in the following media: synthetic medium (9) as used for tuberculin production (strains PN, DT, C); 5 per cent glycerin broth (strain H37Rv); Dubos medium, as described by Bloch (5) (strain H37Rv).

Heat-killed bacilli: Heat-killed tubercle bacilli, a by-product in the routine production of tuberculin, were supplied by the Ministry of Agriculture Veterinary Laboratory, Weybridge (strains PN, DT, C). The microorganisms were killed by three hours' steam treatment (9).

Staining

The following technique was adopted for staining lipid fractions. A small amount (0.5 mg.) was melted on to a strip of filter paper to give a spot 0.2 to 0.5 cm. in diameter. Several different spots could be placed on one strip. Duplicate strips were laid in a Petri dish and Ziehl-Neelsen stain, heated to boiling, was poured on. After ten minutes the strips were well washed with tap water and were covered with 25 per cent sulfuric acid for ten minutes. They were again washed with tap water and one strip of a pair was removed and dried on filter paper. The other was covered with ethanol for twenty minutes, then washed, and dried on filter paper. A fraction which was decolorized by neither alcohol nor acid is referred to as "acid-alcohol fast". A fraction decolorized by alcohol but not by acid is referred to as "acid fast".

Extraction with Petroleum-Ether

Live bacilli: Live bacilli were filtered on a Buchner funnel and then shaken for three minutes with petroleum-ether (boiling point 40° to 60°C.). The extract was separated by centrifuging and the extraction repeated twice. The combined extracts were filtered through a sintered glass filter and distilled to dryness at 37°C. under reduced pressure. The resulting waxy material was dissolved in ether, precipitated by three volumes of methanol, cooled, and centrifuged. The precipitate was re-dissolved in ether and re-precipitated twice. The final precipitate was dissolved in ether, which was then evaporated to dryness.

Steam-killed bacilli: Steam-killed bacilli were extracted as described above. The petroleum-ether extracts were, however, filtered through filter-cel on a Buchner funnel instead of through a sintered glass filter. The final product from extracts of both live and killed bacilli was a near-white waxy material which melted at approximately 30°C. It was microcrystalline and stained acid-alcohol fast. The total yield of material from live bacilli was 0.1 per cent of wet weight of the bacilli, whereas that from killed bacilli was 2.9 per cent. In both cases the proportion precipitated by alcohol was 60 to 65 per cent. The alcohol-soluble material was a soft brown substance corresponding to Anderson's acetone-soluble fats.

Extraction with Ether

Steam-killed bacilli were extracted three times for three minutes with ether. The extract was treated as described above. The yields were of the same order as with petroleum-ether. The properties of the fractions were also similar.

Extraction with Chloroform

Live bacilli: At the end of the growth period required for routine tuberculin production, the medium was withdrawn from the flasks and replaced by chloroform. After shaking, the flasks were allowed to stand at 4°C. for forty-eight hours.[3] (Tubercle bacilli are killed by

[3] We are indebted to Mr. A. B. Paterson, Ministry of Agriculture Veterinary Laboratory, Weybridge, for carrying out this procedure.

standing in acetone, chloroform, or ether for forty-eight hours at 4°C. (Paterson, private communication)). The extract was then separated, filtered through filter-cel, and evaporated to dryness. After re-dissolving in ether, it was precipitated with methanol. The total yield was 7.0 per cent of the wet weight of the bacilli; 75 per cent of the extracted material was precipitated by methanol.

Steam-killed bacilli: Steam-killed bacilli were extracted with chloroform as described for ether and petroleum-ether. The total yield was 4.57 per cent wet weight of bacilli.

Fractionation

The methanol insoluble fractions, obtained as described above, were further fractionated by chromotographic analysis on a column of Florex.[4] The material was dissolved in petroleum-ether and the column was eluted with petroleum-ether–ether mixtures, and ether and ether–acetic-acid mixtures. The weights of material present in successive portions of solvent passing from the column were determined.

All five fractions analyzed this way proved to have present in them the same components, with only slight variations in total recovery of material and proportions of the different components. Recovery was highest from the petroleum-ether extracts and lowest from the chloroform extracts.

Two main components were recovered from the column. The first was neutral, melting point 28° to 33°C., not acid fast, and was microcrystalline. The second was acid, melting point 50° to 55°C., acid-alcohol fast, and was microcrystalline. This component had the properties of mycolic acid. These results are summarized in table 1.

The first fraction was an ester, which was hydrolyzed by heating for ten hours in benzene and alcoholic potassium hydroxide. After hydrolysis, 85 to 95 per cent was ether soluble, crystalline, and melted at 24 to 28°C. Although the ester before hydrolysis stained neither acid nor alcohol fast, after hydrolysis the ether-soluble material stained strongly acid fast. This material was fractionated on a column of Florex; 90 to 95 per cent was recovered in two main fractions. The first was acid, melted at 28 to 30°C., was acid fast, microcrystalline, and represented approximately 45 to 50 per cent of the total yield.

Analysis: Found (Weiler and Strauss) C 79.3 per cent; H 13.3 per cent; m.p. 28 to 30°C. Calculated from mycocerosic acid, C 79.76 per cent; H 13.2 per cent; m.p. 27 to 38°C. (8).

The second fraction was neutral, melted at 68° to 71°C. and was acid fast and microcrystalline. It represented approximately 30 to 40 per cent of the total yield.

Analysis: Found (Weiler and Strauss) C 77.3 per cent; H 13.3 per cent; OCH_3 6.85 per cent; m.p. 68° to 71°C. Calculated for phthiocerol, C 77.8 per cent; H 13.2 per cent; OCH_3 5.75 per cent; m.p. 73 to 74°C. (12).

In no case was any material recovered which corresponded to the phosphatide fraction described by Anderson or to the polysaccharide mycolic acid ester of the chloroform extract. These fractions must be retained by the Florex column. If prolonged extraction with hot acetone is carried out on the methanol precipitates of the petroleum-ether, ether, and chloroform extracts, the extracted material

[4] An aluminium, magnesium silicate, mesh 100. We are indebted to the Floridian Company, Warren, Pennsylvania, for a supply of this adsorbent.

amounts to 75 to 85 per cent, all of which can be recovered from a Florex column. The fraction of the ether and chloroform extracts remaining insoluble in hot acetone yields mycolic acid and polysaccharide on hydrolysis. An even smaller proportion of material remains if an "Anderson phosphatide" preparation is extracted with hot acetone. The residue is about 2 to 7 per cent. This material when hydrolyzed with benzene and potassium hydroxide yields about 60 per cent of ether-soluble material which appears to consist solely of low melting point fatty acids (below 30°C.). It appears probable that the phosphatide and lipopolysaccharide present in the crude precipitates constitute most of the material which cannot be recovered from a Florex column (table 1).

TABLE 1

LIPIDS OF LIVING AND KILLED TUBERCLE BACILLI

	PETROLEUM ETHER		ETHER	CHLOROFORM	
	Live Bacilli	Heat-killed Bacilli	Heat-killed Bacilli	Live Bacilli	Heat-killed Bacilli
Extract, per cent wet weight	0.11	2.9	2.9	7.0	4.7
Methanol precipitate, per cent of extract	66.0	60.0	65.0	75.0	72.0
Neutral fraction, per cent of methanol precipitate	60.0	52.0	43.0	29.0	29.0
Mycolic acid, per cent of methanol precipitate	19.5	34.0	40.0	45.0	42.5
Not recovered, per cent of methanol precipitate	5 to 10	5 to 10	10 to 15	21.0	27.5

Biologic Tests

The fraction corresponding to Bloch's "cord factor" has been tested for biologic activity in guinea pigs and mice.

Guinea Pigs

Five guinea pigs received a total of 7 mg. each of "cord factor": 2 animals were injected intraperitoneally, 2 subcutaneously in the right thigh, and one intramuscularly in the thigh muscles of the right leg. Seven injections of 1 mg. each were given at intervals of two to three days. No loss of weight or toxic symptoms occurred in any of the animals. Ten days after the last injection of "cord factor," the 5 guinea pigs, together with 4 others which had received no "cord factor," were infected subcutaneously with 0.01 mg. virulent human-type tubercle bacilli, strain H37Rv, to determine whether the injections of "cord factor" had produced any enhanced resistance to tuberculous infection. One of the control animals and one which had received "cord factor" were killed eight weeks after infection. Both had early generalized tuberculosis. The remaining control animals died earlier than those which had had injections of "cord factor," but all showed extensive generalized tuberculosis. The difference between the average survival

time of the animals which had received "cord factor" and the control animals was not statistically significant.

Mice

Bloch found that repeated injections of "cord factor" in mice were toxic; whereas a single injection, even of a large amount, produced no toxic symptoms. After a few repeated injections of as small an amount as 0.02 mg., death occurred in the majority of the mice of certain strains. The most susceptible strains in his experience were C57 black and dba. The toxic effect was apparent whether the injections were given intraperitoneally or subcutaneously, dissolved in light paraffin or intravenously dissolved in propylene glycol. The following experiments on mice have been done with three different strains.

Laboratory white mice: Fifteen mice were given seven intraperitoneal injections of 0.1 mg. of "cord factor" dissolved in light paraffin at two- to three-day intervals. None of these died. At autopsy four and one-half months after the last injection, no pathologic lesions were found.

Nine mice had intravenous injections of 0.1 mg. "cord factor" dissolved in 0.1 ml. of light paraffin. Three died shortly after the first injection; 2, after the second injection; 3, after the fourth injection; and one, after the sixth injection. Six mice which had intravenous injections of light paraffin only also died: 2, after the first injection; 3, after the second; and one, after the fourth. It appeared that death in both groups was due to the paraffin and not to "cord factor."

C57 black mice: Ten mice were given eleven intraperitoneal injections of 0.1 mg. "cord factor" at two- to three-day intervals. None died and, when killed three months later, the only abnormality found was some peritoneal adhesions. Three mice were given eight intraperitoneal injections of 1 mg. "cord factor" at two- to three-day intervals. Again, none died and only peritoneal adhesions were present at autopsy four months later.

dba Mice: Six mice were given intravenous injections of 0.1 mg. "cord factor" dissolved in 0.1 ml. of propylene glycol. Injections were given at two- to three-day intervals. One died after four injections. There were no macroscopic lesions but a few giant cells were present in the spleen. Three of the mice developed mummified tails after four injections, clearly from the irritative effect of the propylene glycol. The remaining 2 had six injections before the condition of their tails made further intravenous injections impossible. The 5 mice were killed five months after the last injection. No abnormality was found at autopsy.

These animal experiments failed to show any toxic effects from the petroleum-ether extracts of virulent tubercle bacilli, nor was it possible to demonstrate any detoxifying effect of petroleum-ether extraction on virulent tubercle bacilli. By guinea pig experiment it was shown that the bacilli after extraction were viable and virulent.

DISCUSSION

The results described above, which are in close accord with the work of Asselineau and Lederer (4), show that the somewhat complex picture, drawn by Anderson (1), of the lipids of the tubercle bacillus can to some extent be simpli-

fied. Every solvent used has extracted from live or dead bacilli four main components:

(*1*) a fraction soluble in cold acetone or methanol consisting of low melting point fatty acids; (*2*) an ester of phthiocerol with fatty acid; (*3*) free mycolic acid; (*4*) a fraction insoluble in hot acetone which contains esters of carbohydrate with fatty acids, i.e., Anderson's phosphatide and the polysaccharide ester of mycolic acid.

Anderson and co-workers have isolated several fatty acids from tubercle lipids, e.g., palmitic and stearic acids, tuberculostearic acid, phthioic acid, mycocerosic acid, as well as unsaturated fatty acids. During chromatographic analysis, small amounts of material may be found eluting separately from the main components but with similar properties. It is probable that these may be esters of phthiocerol with other fatty acids.

Asselineau and Lederer (4) showed that the property of acid resistance of mycolic acid depended on the presence of a hydroxyl and a free carboxyl group. Any derivative with which these groups are blocked will only stain acid and alcohol fast if the critical groups are freed during the staining process. The only fractions described in this paper which stain acid and alcohol fast all contain free mycolic acid which is found equally in the extracts made from live and killed bacilli with petroleum-ether, ether, and chloroform.

Sabin (11) has tested lipid fractions, supplied by Anderson, for biologic reactions. She has shown that phthioic acid or its ester, present in the phosphatide fraction, produced epithelioid cells. Phthioic acid can be found, in small amounts, in most of the fractions described by Anderson (10). The wax (? mycolic acid ester) induced the formation of foreign-body giant cells. Raffel (10) showed that, although the lipo-polysaccharide fraction has no biologic activity per se, it appears to control the type of allergic response given by an accompanying protein.

Bloch's claim that the petroleum-ether extract of live virulent tubercle bacilli was in part responsible for the virulence of the bacilli, and that it was in itself toxic to certain strains of mice, has not been confirmed. Choucroun and associates (7) have shown that, as far as the effect of tubercle bacilli on the rate of migration of leukocytes is concerned, the difference between virulent and avirulent strains is quantitative, not qualitative. They claim that the polysaccharide ester of mycolic acid has an effect on leukocytes similar to that of the whole bacilli. As is described here, it has not been possible to find any toxic effect following injection of the petroleum-ether extract of live virulent tubercle bacilli into susceptible strains of mice or into guinea pigs. Nor was there any significant effect on the severity of infection by human-strain bacilli following injection of the extract.

SUMMARY

Live, heat-killed, and organic solvent-killed tubercle bacilli were extracted with petroleum ether, ether, and chloroform.

The extracts were fractionated according to solubility in solvent mixtures, followed by chromatographic analysis.

All the extracts were found to contain the following components in varying proportions: (a) acetone-soluble fats; (b) free mycolic acid; (c) an ester of mycocerosic acid with phthiocerol; (d) esters of polysaccharide with mycolic acid and other fatty acids.

The petroleum-ether extract of live virulent tubercle bacilli was found to have no toxicity for mice and guinea pigs; nor did injection of the extract confer any protection against subsequent infection with tubercle bacilli.

SUMARIO

Los Lípidos de los Bacilos Tuberculosos Vivos y Muertos

De bacilos tuberculosos vivos, matados al calor y matados con solventes orgánicos se obtuvieron extractos con éter petrólico, éter y cloroformo.

Esos extractos fueron fraccionados conforme a su solubilidad en mezclas solventes y después sometidos a análisis cromatográfico.

En todos los extractos se encontraron los siguientes componentes en variadas proporciones: (a) grasas solubles en acetona, (b) ácido micólico libre, (c) un éster del ácido micocerósico con ftiocerol y (d) ésteres de polisacáridos con ácido micólico y otros ácidos grasos.

El extracto obtenido con éter de petróleo de bacilos tuberculosos virulentos vivos no mostró toxicidad para los ratones y cobayos, ni tampoco otorgó la inyección del mismo la menor protección contra la infección subsiguiente con bacilos tuberculosos.

RESUME

Lipides des bacilles tuberculeux vivants ou tués

Un extrait de bacilles tuberculeux vivants, tués par la chaleur ou par un solvant organique a été obtenu avec l'éther de pétrole, l'éther et le chloroforme.

Ces extraits étaient fractionnés selon leur solubilité dans les mélanges de solvants; ils étaient ensuite analysés par la méthode chromatographique.

Tous ces extraits contenaient, en proportion variée, les constituants suivants: (a) des graisses solubles dans l'acétone, (b) de l'acide mycolique libre, (c) un ester de l'acide mycocérosique avec du phthiocérol, (d) des esters de polysaccharide associés à l'acide mycolique et à d'autres acides gras.

L'extrait éther de pétrole de bacilles vivants virulents a été trouvé dépourvu de toxicité pour la souris et le cobaye; d'autre part l'injection d'extrait n'a pas conféré l'immunisation contre l'inoculation subséquente par le bacille tuberculeux.

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A BACTERIOLOGIC STUDY OF RESECTED TUBERCULOUS LESIONS[1]

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INTRODUCTION

The microscopic study of random sections from specimens of surgically resected tuberculous lung tissue not infrequently shows areas of neutrophilic infiltration in necrotic lesions which have not sloughed, and usually reveals a similar picture in open sloughing foci. In the solid necrotic focus it is unusual to be able to demonstrate in tissue sections bacteria of any sort in the areas of neutrophilic infiltration. In the open sloughing lesions, acid-fast bacilli only are usually demonstrable and these may or may not be found in association with the neutrophilic exudate. A clinical concept prevails that neutrophils are associated with "pus-producing" bacterial infections rather than with tuberculous infection. This concept is frequently noted in the clinical records of tuberculous patients, for considerable stress is given to the occurrence of an "upper respiratory infection" just prior to the first diagnosis of an active pulmonary tuberculosis and to relapses of the disease. Because of the finding of a predominance of neutrophils under certain circumstances in resected tuberculous lesions and because of the concept that "secondary" infections often play a significant role in the clinical behavior of pulmonary tuberculosis, a study was undertaken to determine the bacteriologic content of lesions that became available from surgically resected tuberculous lung tissue.

In the initial observations, cultures for microorganisms other than tubercle bacilli were of prime interest. As the study progressed, however, an inability to obtain growth of *M. tuberculosis* from samples which contained numerous acid-fast bacilli became the major and continuing problem. In the present report, the results of cultures for microorganisms other than tubercle bacilli and the results of smear examinations and cultures for *M. tuberculosis* are presented and the problem of failures to obtain growth of *M. tuberculosis* is discussed.

MATERIALS AND METHODS

Specimens of surgically removed tuberculous lung tissue from 72 patients were used. These specimens came from 131 different lobes of lungs.

To obtain material for bacteriologic study, the tuberculous lesion was incised with a knife which was sterilized in an open flame. If a focus was sufficiently softened, its contents were removed by sterile swabs. Solid lesions were macerated and homogenized in a sterile Tenbroeck Glass Tissue Grinder. Cultures for bacteria other than *M. tuberculosis* and for fungi were made by direct planting on a variety of solid and liquid media. In most instances both aerobic and anaerobic conditions were used. In the early part of the study all material used for culture of *M. tuberculosis* was digested with 3 per cent sodium hy-

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droxide and the concentrate, after neutralization, was planted on American Trudeau Society medium.[3] After it was found that no bacteria other than tubercle bacilli were obtained, it became a routine procedure to plant the material directly without digestion on American Trudeau Society medium.

The material for bacteriologic culture was taken from tuberculous lesions of different types. Material was obtained with sterile swabs from 29 open cavities. Fifty-eight lesions were considered to be filled-in cavities, and the major portion of the necrotic debris was removed with sterile swabs. In 122 specimens the lesions were regarded as solid necrotic foci, for, although material for study was removed with a sterile swab in many instances, the major portion of the lesion was in a solid state. Approximately one-half of the lesions of this type were macerated and homogenized in a sterile tissue grinder and the "homogenates" were used for smear and culture.

RESULTS

Cultures for bacteria other than *M. tuberculosis* were performed on 94 specimens. Of these, 23 were open cavities, 33 were filled-in cavities, and 38 were solid necrotic lesions. All of the cultures were negative for bacteria other than tubercle bacilli. Growth of *M. tuberculosis* was obtained from every open cavity, from 27 per cent of the filled-in cavities, and from 20 per cent of the solid necrotic lesions.

In addition, cultures for bacteria other than tubercle bacilli were made from material taken from 13 open cavities and from 5 solid lesions obtained at necropsy on 7 tuberculous patients. Growth was obtained from all but 2 of the specimens. *Streptococcus*, pneumococcus, *Staphylococcus*, *E. coli*, *Proteus*, and *Monilia* were among the different microbial species noted. The contrast between the results of the cultures from surgical and from necropsy specimens is discussed below.

Smears of the material which was used for the culture of *M. tuberculosis* were seldom examined for acid-fast bacilli during the first several months of the study, and no animal inoculations were done. Nevertheless, smears from 5 filled-in cavities revealed acid-fast bacilli in considerable numbers, and no growth of *M. tuberculosis* was obtained from these specimens. The 5 lesions had been removed from 2 tuberculous patients who had been receiving streptomycin and para-aminosalicylic acid (PAS) therapy continuously for an eighteen-month period. This experience led to the routine use on all subsequent specimens of smear examination, of animal inoculation, and of culture.

The results of smear examination and of culture of the material from 130 specimens are presented in tables 1 and 2. Smears from 79 previous specimens had not been done consistently and they are not included in the tables. As may be seen in table 1, acid-fast bacilli were present in three-fourths of all of the specimens examined, and there was a considerable variation in the numbers of bacilli. Larger numbers of bacilli commonly were found in open sloughing lesions. In smears from open cavities, a Gaffky IV, or higher, was found in 47 per cent; from filled-

[3] This medium is an egg-yolk–potato–glycerin–malachite green medium which has been recommended by the Laboratory Committee of the American Trudeau Society.

in cavities, the percentage was 29; in material from solid necrotic lesions only 14 per cent gave a high Gaffky count.

The results of smear examinations and of cultures for *M. tuberculosis* from samples from different types of lesions are presented in table 2. Although acid-fast bacilli were found in smears in a high proportion of all types of lesions, growth of *M. tuberculosis* was obtained quite consistently only from open sloughing lesions.

During the entire study, 209 samples, including the specimens from which smears were not examined, were cultured for *M. tuberculosis*. There were 29 open cavities with growth from 24 (83 per cent); 58 filled-in cavities with growth from

TABLE 1

RESULTS OF SMEAR EXAMINATIONS FOR ACID-FAST BACILLI OF MATERIAL FROM 130 LESIONS IN SURGICALLY REMOVED LUNG TISSUE

	NUMBER	PER CENT
Negative	35	26.9
Gaffky I	35	26.9
Gaffky II and III	32	24.6
Gaffky IV or more	28	21.6

TABLE 2

COMPARISON OF SMEARS AND CULTURES FOR M. TUBERCULOSIS IN DIFFERENT TYPES OF LESIONS FROM 130 LESIONS IN SURGICALLY REMOVED TISSUE

	NUMBER	PER CENT
Open cavities (15)		
Smears positive	12	80.0
Cultures positive	15	100.0
Filled-in cavities (45)		
Smears positive	37	82.2
Cultures positive	5	11.0
Solid lesions (70)		
Smears positive	46	65.7
Cultures positive	6	8.5

14 (24 per cent); and 122 solid necrotic lesions with growth from 9 (7 per cent). In all instances in which growth was obtained from specimens from closed lesions, the number of colonies obtained represented only a small fraction of the numbers of bacilli which had been planted, as estimated from the smears. Although examinations of smears for acid-fast bacilli were not made in 79 instances, it is probable, from the data in table 2, that at least two-thirds of all specimens would have shown their presence.

COMMENT

The culturing of tuberculous lesions for bacteria other than *M. tuberculosis* was undertaken to clarify the frequent finding of considerable numbers of neu-

trophils in microscopic sections. The negative results obtained would seem to indicate that resected tuberculous lesions are extraordinarily free from "mixed" infections. Perhaps this may be due to the fact that all of the patients had received some sort of antimicrobial therapy. It seems rather paradoxical, however, that all bacteria other than tubercle bacilli would be destroyed by drugs administered because of their activity against the tubercle bacillus and that growth of the latter organism was obtained in 40 per cent of the samples. This applies particularly to open cavities which would be most likely to become "secondarily" infected. Cultures at necropsy of tuberculous lesions which were similar to those present in surgically resected lungs showed that a mixed bacterial population frequently was present. In 3 of the patients who came to necropsy, chemotherapy was in effect at the time of death.

Patients who succumb to tuberculosis are often in a debilitated condition for weeks prior to death, and tissues in such a state are much more susceptible to infections of various types. In such circumstances, it does not seem logical to apply the bacteriologic findings of necropsy material to all tuberculous disease. It is believed that the bacteriologic flora found in the resected specimens indicates accurately the general condition to be expected in progressive pulmonary tuberculosis. It seems probable that the presence of purulent sputum in a tuberculous patient does not indicate a "mixed" infection. In the process of sloughing of necrotic tuberculous lesions, the neutrophil apparently performs the same function that it does in the sloughing of necrotic lesions induced by other causes. Sloughing of necrotic tuberculous lesions is a common occurrence, and the liquefaction preparatory to sloughing is prominently participated in by the neutrophil. It would appear to be unnecessary, and perhaps erroneous, to interpret a progression of pulmonary tuberculosis as an effect instigated by an intercurrent infection.

The inability to obtain growth of *M. tuberculosis* from samples which on direct smear revealed acid-fast bacilli will be discussed, rather to present the problem than to give an answer. In the culturing of sputum from tuberculous patients, it has been unusual in the writers' experience to fail to obtain growth of *M. tuberculosis* if acid-fast bacilli were demonstrated in smear preparations of the material to be cultured. Moreover, it has also been unusual to fail to obtain growth of *M. tuberculosis* from open cavities either from necropsy material (1) or from surgical specimens. In the early part of the present study, smears of the material taken for culture for *M. tuberculosis* were not done, as it was assumed from previous experience that cultures would yield more accurate data than smears. On two occasions, however, smears which were made from the contents of filled-in cavities showed numerous, well-stained acid-fast bacilli, and no growth was obtained on culture. The particular interest in this situation was that these specimens were resected from 2 tuberculous patients who had been receiving continuous streptomycin and PAS therapy for eighteen months; in each instance sputum cultures had failed to yield any growth of *M. tuberculosis* for more than a year. Prior to that period, bacilli were easily and consistently grown from sputum samples of these patients.

The data presented in table 2 show that 73 per cent of the samples contained acid-fast bacilli and that growth of *M. tuberculosis* was obtained in only 20 per cent. There were no failures to obtain growth from open sloughing lesions; however, from "closed" lesions, i.e., filled-in cavities and necrotic lesions which had not sloughed, which revealed bacilli in smear preparation, growth was obtained in only 13 per cent. It would appear that the "closing" of a tuberculous lesion profoundly affects the tubercle bacillus. Since all of the material studied came from patients who had been treated chemotherapeutically and since it is a common occurrence for cavities to "close" during such therapy, one may surmise that the changed status of the tubercle bacillus is induced by the chemotherapeutic agents employed. The beneficial effect of chemotherapeutic regimens in the treatment of tuberculous patients is beyond question. It must be recognized, however, that the manner in which such regimens affect the tubercle bacillus remains unknown. Among the specimens studied there were 2 "closed" lesions, each of which was 3 cm. in diameter, which came from patients who had been treated chemotherapeutically for less than a month before resection was done. One of these lesions was a filled-in cavity and the other was a necrotic lesion which had never sloughed. Both of the specimens showed numerous acid-fast bacilli in smear preparations and no growth of *M. tuberculosis* was obtained from either specimen. This observation would suggest that the changed status of the tubercle bacillus perhaps may be related more to the condition within tuberculous lesions than to the effect of a chemotherapeutic agent.

It may be assumed that bacilli which will not grow on artificial media are dead; it is important to bear in mind, however, that this is only an assumption. That the phenomenon of non-culturable tubercle bacilli may not be related directly to chemotherapy is borne out by Canetti (2) who, on occasion, failed to obtain growth from necropsy specimens which contained many bacilli and which came from patients who had not been treated chemotherapeutically. The present writers are in agreement with the following statement made by Canetti:

> There exist in numerous tuberculous lesions of man some bacilli which when inoculated on artificial media do not produce colonies at the moment. It is possible that a greater number of these bacilli are dead and as to the others which are still alive their ability to reproduce is greatly lessened. Concerning the acid-fast bacilli which we see in the tuberculous lesion, there are those that are dead and subject to disintegration; others that are living but are unable to reproduce, and some at the time are living and are plainly able to reproduce.

If the bacilli in question are dead, they still retain their morphologic and staining characteristics. The present data show that no bacilli were demonstrable in smear preparations from approximately one-fourth of the specimens, and in an approximately equal portion bacilli were present in large numbers, even in colony formation. These masses of bacilli are found deep within necrotic lesions which have never sloughed, as well as in "closed" cavities. In the unsloughed lesions, it seems evident that the bacilli have reproduced in the necrotic tissue. In the filled-in cavities, it is not possible to be certain that the bacilli have reproduced after the cavities have closed, for it is not unusual to find large numbers of bacilli

in debris that is sloughing from cavities, as well as in the necrotic tissue which forms the inner lining of cavities. Masses of bacilli, often in colony formations, are present in both unsloughed and filled-in necrotic lesions in persons who have received no antimicrobial therapy as well as in those who have received such therapy. If it be assumed that dead tubercles can remain intact in necrotic lesions for an undeterminable period of time, then it would seem paradoxical to find that, in two unsloughed necrotic lesions which morphologically were similar, one lesion revealed no bacilli and the other contained bacilli in large numbers.

A considerable amount of work is in progress to determine the pathogenicity of the bacilli which will not grow on artificial media. In a few completed tests, guinea pigs which were inoculated with considerable material which contained numerous bacilli failed to show evidence of tuberculous disease when sacrificed six months after inoculation. The final assessment of pathogenicity will have to await the accumulation of a considerable volume of data.

It might be assumed that loss of pathogenicity would indicate death of the bacilli. A study of a streptomycin-dependent strain of *M. tuberculosis* is of interest in this connection (3). This strain was nonpathogenic when grown on medium which contained a high concentration of streptomycin. In 160 subcultures from growth on streptomycin-containing medium (15 γ or more of streptomycin per ml.), only one colony grew on medium which contained no streptomycin. Subcultures from growth on medium which contained only 3.5 γ of streptomycin per ml., however, yielded one or more colonies in one-fourth of the cultures on streptomycin-free medium, and the organisms so cultured were fully pathogenic. This illustrates the versatility of the tubercle bacilli and suggests that caution be used in the interpretation of pathogenicity tests in relation to viability of this organism.

It is well known that tuberculous patients can remain clinically well for years with the presence of stationary shadows on the chest roentgenogram without demonstrable evidence of cavity formation and with no demonstrable tubercle bacilli in sputum or gastric contents. Moreover, it is well known that such tuberculous patients often experience relapses of their pulmonary disease. The bacteriologic study of the resected "closed" tuberculous lesions shows that they commonly harbor bacilli which show normal morphologic and staining characteristics. Considering both the well-known clinical facts and the demonstration of tubercle bacilli in resected closed lesions, it would seem that these organisms commonly can remain for long periods of time within the closed necrotic lesion without giving rise to clinical illness. A slough of the necrotic lesions which contain the bacilli may well be responsible for the liberation of the organisms and the recrudescence of clinical disease. Unfortunately there are no data relative to the status of the tubercle bacilli during the long period of incarceration.

The bacteriologic problem found by the study of the resected lung specimens requires solution before it will be possible to evaluate the effect of long-term chemotherapy in tuberculosis. From the present preliminary studies, it would appear to be a difficult problem to solve. Perhaps the tubercle bacillus may be able to exist at a survival level for a long time. Moreover, after it has become adjusted

to this environment, difficulty may be experienced in regaining its ability to grow rapidly and continuously in the artificial environment of the culture tube. The pathogenicity of these strains of tubercle bacilli may also conceivably be affected by the accommodation to incarceration within the necrotic lesion. If these conditions do exist, it is conceivable that the technical procedures which now are in use to obtain growth of the bacillus and to determine its pathogenicity may be totally inadequate. It is recognized that these remarks are of a purely speculative nature; however, they are no more so than an assumption that large numbers of *dead* bacilli within necrotic lesions may retain their characteristic morphologic and staining characteristics for a long and undeterminable time. It is quite evident that this problem can be solved only by working with material from necrotic lesions, preferably those obtained from persons who have received either no chemotherapy or chemotherapy for no longer than a few days. It will also be essential to include in the study necrotic lesions of various sizes and of different ages. The importance of obtaining a solution to this problem cannot be overemphasized.

SUMMARY

Cultures of 94 resected tuberculous lesions failed to yield growth of any bacteria other than tubercle bacilli, and yielded growth of *M. tuberculosis* in 40 per cent. It would seem that tuberculous lesions are extraordinarily free from mixed infection. It would also appear that neutrophils play a significant role in the process of liquefaction of tuberculous lesions prior to the process of sloughing.

The failure to cultivate *M. tuberculosis* from material taken from resected tuberculous lesions which contain numerous acid-fast bacilli is presented, and the implications of the experimental finding are discussed.

SUMARIO

Estudio Bacteriológico de las Lesiones Tuberculosas Resecadas

Los cultivos de 94 lesiones tuberculosas resecadas no rindieron colonias de ninguna forma secundaria de bacterias ni rindieron colonias del *M. tuberculosis* más que en 40 por ciento. Parece, pues, que las lesiones tuberculosas se encuentran inusitadamente exentas de infección mixta. Además, parece que los neutrófilos desempeñan un papel importante en la ocurrencia de licuación de dichas lesiones antes de tener lugar el esfacelamiento.

Menciónase la incapacidad para cultivar el *M. tuberculosis* del material obtenido de lesiones tuberculosas resecadas que contiene numerosos bacilos ácidorresistentes. Los comentarios ofrecidos se proponen plantear el problema más bien que adelantar la solución.

RESUME

Une étude bactériologique de lésions tuberculeuses réséquées

Les cultures de 94 pièces provenant de lésions tuberculeuses réséquées n'ont donné aucune colonie de bactérie de type secondaire, elles ont donné une culture de *M. tuberculosis* dans une proportion de 40%. Il semble que les lésions tuberculeuses soient étonnamment libres d'infection mixte. Il semblerait aussi que les neutrophiles jouent un rôle significatif quand il s'est produit une liquéfaction des lésions tuberculeuses antérieure à l'excision.

L'impossibilité d'obtenir une culture de *M. tuberculosis* à partir de matières prélevées

sur des lésions tuberculeuses réséquées, riches en bacilles acido-résistants, est signalée. Les commentaires constituent plutôt un exposé du problème que sa solution.

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A STUDY OF THE TUBERCLE BACILLUS IN RESECTED PULMONARY LESIONS[1]

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INTRODUCTION

The use of chemotherapeutic agents in combination with surgical excision procedures in the treatment of tuberculosis has enjoyed increasing popularity in the past year. Recently, however, much attention has been diverted from the pathologic study of the resected specimens to bacteriologic investigation. This was brought about by the common finding, in many cases in which antimicrobial therapy had been used, that the lesions in resected lung specimens may contain many tubercle bacilli which do not grow on culture or produce disease in guinea pigs.

It is obviously of great clinical importance to determine whether this phenomenon is due to natural causes associated with healing or is a direct result of antimicrobial therapy. The writers have had the opportunity to study the bacteriology of the lesions from 3 tuberculous patients who had had no preoperative chemotherapy. Included also in the present report are the bacteriologic findings from other cases in which resection was performed after varying periods of chemotherapy as well as experimental bacteriologic procedures which were carried out in connection with this problem.

PLAN OF INVESTIGATION

The material studied consisted of 50 specimens which were removed during excisional surgery for tuberculosis on 28 patients. The specimens ranged in size from a small wedge to an entire lung. One specimen was an encapsulated chest-wall abscess. In centering attention on the bacteriologic approach, it was necessary to forego certain pathologic studies. Accordingly, no details of the histologic character of the lesions in many of the small specimens are presented.

The gross specimen, in a sterile receptacle, was sent to the laboratory without delay and was handled aseptically throughout. One or more palpable lesions were removed for examination. In the case of an inspissated cavity or large encapsulated lesion, all of the caseous material and curettings of the cavity wall were transferred to a tube containing a small quantity of physiological saline solution. The resulting suspension was shaken to break up any large particles. Small, hard, encapsulated nodules were removed, together with some of the surrounding, apparently healthy, lung tissue, and were macerated in a tissue-grinding instrument. The macerated material was then suspended in physiological saline solution.

The routine bacteriologic examination included thorough microscopic study of stained films as well as culture on the solid medium used routinely for culturing tubercle bacilli and on oleic-acid-agar and liquid Tween[2]-albumin media. In addition, 1 or 2 ml. of the suspension were injected into the groin of a healthy guinea pig.

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[1] From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

[2] Tween 80 is the proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

Culture tubes showing no growth were not discarded until after a minimum incubation time of three months. Guinea pigs were tested with tuberculin at one-month intervals and, if the cutaneous reaction was negative, they were not sacrificed until three months after inoculation. All positive cultures obtained were tested for sensitivity to streptomycin and para-aminosalicylic acid (PAS).

The failure to obtain growth by the conventional methods suggested possible alteration of the bacilli by adsorption of toxic substances or by a change in nutritional or environmental requirements. To investigate these considerations, whenever sufficient material was available, media were employed which contained starch, charcoal, albumin, and other efficient adsorbing agents. Prolonged incubation at 37°C., incubation of duplicate sets of cultures at temperatures other than 37°C., as well as varying of the pH of the media, were also carried out.

Some of the caseous materials which did not contain frank blood were assayed chemically for the presence of PAS and biologically for streptomycin. The latter was done by determining any inhibitive effect against a streptomycin-sensitive organism and also by adding the material to medium inoculated with a streptomycin-dependent strain of *Mycobacterium ranae*, which requires only a small amount (0.05 to 10 γ per ml.) of streptomycin for growth.

RESULTS

The cases have been separated into three groups. The initial group consisted of 17 patients from whom 27 lesions were studied. These patients had received continuous therapy until surgery, and the regimen is designated as *original treatment*. These cases are summarized in table 1. The data under *preoperative sputum* refer to the cultural findings for the four preoperative months, and the findings under *lesion* refer to the bacteriologic study for acid-fast bacilli.

In table 2 the findings are presented for a group of 8 patients with 15 studied lesions who had more than one course of treatment, with intervening periods without treatment.

In table 3 are reported the results in 3 patients in whom 8 lesions were studied and who had no streptomycin or PAS therapy prior to surgery.

It should be noted that in the *original treatment* group (table 1) the duration of preoperative drug therapy ranged from $2\frac{1}{2}$ to $8\frac{3}{4}$ months. In all of the cases except one, the sputum was negative for *M. tuberculosis* by culture at the time of operation. It should be re-emphasized that it was necessary to sacrifice any histologic study of the smaller lesions in order to achieve the bacteriologic aims as outlined in the plan of investigation. It is obviously easy to identify grossly an open cavity with a draining bronchus, but to differentiate accurately an unemptied caseous area from a filled-in cavity requires demonstration of the alveolar structures, and is irrefutably possible only by histologic study. For this reason no effort has been made to differentiate these last two types of lesion. It can be stated, however, that virtually all of the lesions were caseous areas of these two types.

It should be noted that acid-fast bacilli were demonstrated in the stained films from the specimens of 16 of the 17 patients in the *original treatment* group, and yet positive cultures were obtained in only 4 patients. These bacilli were susceptible to streptomycin and PAS except the strain obtained from one patient (Case 7) who was known to have been infected with streptomycin-resistant tubercle bacilli.

The results in the *re-treatment* group are reported in table 2. The group is too small for adequate comparison with the *original treatment* group, but 2 patients yielded the finding of nonviable organisms on the basis of positive findings on smear, with negative results on culture and guinea pig inoculation. In the lesion from only one patient was it impossible to demonstrate acid-fast bacilli micro-

TABLE 1

ORIGINAL TREATMENT CASES

CASE NUMBER	TREATMENT			PREOPERATIVE SPUTUM	LESION		
	Duration Prior to Surgery	Daily Dosage in Grams			Smear	Culture	Guinea Pig Inoculation
		SM	PAS				
1	3½ months	1.0	12	0000	X*	negative	not done
2	7½ months	1.0	12	0000	negative	negative	negative
3	5½ months	0.5	9	0000	I	negative	negative
4	6½ months	0.5	12	0000	II	negative	negative
5	3½ months	0.9	12	0000	II	negative	negative
6	5¾ months	1.3	12	+000	V	negative	negative
					III	negative	negative
					negative	negative	negative
7	8¼ months	1.2	12	++++	II	negative	negative
					negative	negative	negative
					II	+	+
8	6 months	1.1	12	+000	II	+	+
					negative	negative	negative
9	5½ months	1.5	12	0000	III	negative	negative
10	7 months	1.1	12	+000	V	+	+
					negative	negative	+
11	3½ months and 18 days	0.5	9	0000	II	negative	negative
					negative	negative	negative
12	6 months	0.5	9	0000	negative	negative	negative
					I	negative	negative
13	8¼ months	1.0	12	0000	I	negative	+
					II	negative	+
					negative	+	+
14	8¾ months	1.0	12	0000	II	negative	negative
15	4¼ months	1.2	12	0000	III	negative	negative
16	5 months	1.0	12	0000	III	negative	negative
17	7 months	1.0	12	+000	II	negative	negative

* Gaffky count.

scopically, and guinea pig inoculation was positive for tubercle bacilli in this instance. The tubercle bacilli cultured from the lesions in this group were susceptible to streptomycin and PAS *in vitro*.

As noted in table 3, three patients had excision therapy without preoperative streptomycin or PAS therapy. It is of interest to describe briefly the problems presented by these patients:

Case 1. The patient (L. G.) was a 38-year-old man whose tuberculosis was diagnosed roentgenographically in 1939. The lesion remained unchanged until 1945, when an exacerbation

TABLE 2

RE-TREATMENT CASES

CASE NUMBER	TREATMENT			PREOPERATIVE SPUTUM	LESION		
	Duration Prior to Surgery	Daily Dosage in Grams			Smear	Culture	Guinea Pig Inoculation
		SM	PAS				
1	91 days	1.0	10	0000	I*	negative	+
	77 days	1.0	12		II	+	+
	2½ months	—	12		negative	negative	+
	1 week	1.0	12				
2	90 days	1.0	—				
	1 month	—	?		V	negative	negative
	3 months	1.0	12	++00	VI	negative	negative
3	91 days	Combined	2				
	77 days	1.0	12				
	5½ months	—	12		negative	negative	+
	15 days	1.0	12	0+00	negative	negative	+
4	6 weeks	b.i.d.	—		VI	+	+
	3 months	1.0	12	+++0	V	+	+
					negative	+	+
5	6 weeks	?	—				
	2 weeks	—	?				
	4 weeks	?	?				
	6 months	1.0	12	++++	IX	+	+
6	6 months	1.0	12				
	101 days	—	12				
	3 months	1.0	12	++++	VI	+	+
7	Total of						
	11 months	0.5	9	0000	I	negative	negative
					II	negative	negative
8	6 months	1.0	12				
	5½ months	—	12	+??+	VI	+	+
	4½ months	1.0	12				

* Gaffky count.

TABLE 3

NON-TREATMENT CASES

CASE NUMBER	PREOPERATIVE SPUTUM	LESION		
		Smear	Culture	Guinea Pig Inoculation
1	0000	V*	1 colony	+
			+	
		VII	negative	negative
		II	negative	negative
		II	negative	negative
		II	negative	negative
2	no sputum	negative	negative	negative
3	0000	II	negative	negative
		negative	+	+

* Gaffky count.

resulted in a nine-month period of rest in a tuberculosis hospital. His condition was satisfactory until February 1951, when he had another exacerbation which resulted in hospitalization. At this time, numerous, fairly dense, nodular shadows above the third left anterior rib were visible on the chest roentgenogram. Planigrams showed no cavity. Sputum was negative for tubercle bacilli by all methods on repeated examination. At operation the disease was found localized in one segment of the left upper lobe, and the diseased portion of the segment was removed. When the specimen was opened, many diseased areas containing calcium were found, and liquid pus was noted in one area.

Five of the lesions were studied bacteriologically. All were positive for acid-fast bacilli by smear; yet only one of the specimens was positive for *M. tuberculosis* by culture and this showed but one colony. Although the patient's preoperative course was marked by negative sputum findings, a few acid-fast bacilli were found on smear of intratracheal secretions aspirated during the operation, but no growth was obtained on cultures.

Case 2. The patient (N. A.) was a 44-year-old woman who had an exploratory thoracotomy because of the presence of an undiagnosed, solid, round mass in the right lower lobe which was removed by wedge resection. The mass measured approximately 4 cm. in diameter and there were eight to ten sharply defined adjacent nodules, none of which exceeded 0.5 cm. in size. The mass was made up of firm, yellowish-gray tissue with a number of concentric laminations and scattered foci of black pigment. The smaller adjacent nodules proved to be minute caseous foci. Histologically, the large lesion was diagnosed as tuberculoma.

Stained sections failed to reveal acid-fast bacilli, and cultures and animal inoculation of material from the lesion were negative for *M. tuberculosis*.

Case 3. The patient (P. McS.) was a 23-year-old woman who had her first symptoms of tuberculosis in 1947. At that time she had extensive disease in the right lung with cavitation, and sputum was positive for acid-fast bacilli. On a program of bed rest she showed marked resolution of her disease, but was referred for surgical exploration because of a dense shadow noted in the right anterior chest. Exploration was indicated to investigate this shadow and at the same time to palpate the lung to determine if any disease residua should be removed. At operation the mass anteriorly was found to be a tuberculous abscess and the entire area was removed. Palpation of the lung revealed a string of eight nodular densities in the lower lobe measuring from 3 to 8 mm. These areas were removed and found to be sharply defined caseous foci with fibrous capsules.

Material from the abscess was studied bacteriologically and revealed acid-fast bacilli microscopically, but was negative by culture and guinea pig inoculation for tubercle bacilli. Material from one of the nodular densities showed no acid-fast bacilli microscopically, but was positive for tubercle bacilli both by culture and guinea pig inoculation.

The bacteriology in studies on media containing the various adsorbing agents described above was not rewarding. No growth was obtained on these special media in any instance in which it was not also present on the media used routinely.

DISCUSSION

The present report gives the results of bacteriologic study of resected tuberculous specimens for the presence of tubercle bacilli. The data confirm the findings of others that acid-fast bacilli may be found microscopically in surgical specimens

from the majority of patients who had streptomycin and PAS therapy preoperatively, but that these bacilli fail to grow in suitable media and do not produce disease in guinea pigs. This finding is not limited to patients who have had prolonged drug treatment but is also noted in some patients who had relatively short periods of treatment. While antimicrobial therapy might be assumed to be the causative factor in these cases, the presence of non-culturable tubercle bacilli in the lesions of 2 patients who had not received streptomycin or PAS must be attributed to the natural defenses of the host. In view of this fact, it is difficult to determine what part is played by the drugs in those cases in which preoperative antimicrobial therapy was given.

Bacteriologic study of tuberculous lesions prior to the advent of streptomycin is limited to study of post-mortem material and, unfortunately, most of the early work contains no correlation of the study of the stained smear with culture or animal inoculation. Sweany (1, 2, 3), however, has demonstrated acid-fast bacilli on smear and subsequent failure to obtain growth with the same material on culture or to produce disease in animals. It is his opinion that these bacilli are dead and that the death curve of tubercle bacilli rises sharply after the first year of age of the tubercle until virtually none are found in lesions five or more years old. Canetti (4) has also reported the observation that acid-fast bacilli have been noted in caseous material and that this material has been negative for tubercle bacilli by culture. These reports simply indicate that tubercle bacilli in lesions can naturally lose their ability to reproduce and that further study is indicated to determine any correlation of this phenomenon with the type and age of the lesion. Material for this work is available in post-mortem examinations and in surgical specimens removed from patients who have not had preoperative streptomycin or PAS therapy.

The fact that non-culturability can be independent of streptomycin therapy is clear but, when it occurs following the use of this drug, the possibility of a drug effect must be considered. The 2 patients who had non-culturable organisms without a history of streptomycin treatment had lesions of long standing which were circumscribed and without an obvious open bronchial communication. This type of disease was in marked contrast with that in many of the treated cases in which disease of more recent onset was present and was accompanied by open cavities with patent bronchi in some instances. This suggests the possibility of a direct drug effect on the bacilli.

On the other hand, the action of the drugs on tubercle bacilli in old encapsulated lesions is difficult to assess. The writers have been unable, with several attempts, to detect either streptomycin or PAS in the centers of the caseous material in these lesions. In fact, the one instance in which streptomycin could be demonstrated was in an open cavity. Some workers (5) have concluded that the recovery of streptomycin-resistant bacilli from the unsloughed lesions of patients taking streptomycin alone is evidence for the presence of the drug in these lesions. Streptomycin-resistant tubercle bacilli were found only once in the present series of cases, and the patient was known to have been infected with a resistant strain.

In the circumscribed isolated tuberculous lesion without open bronchial com-

munication, lack of essential nutrients or unfavorable physical and chemical conditions might reasonably be held responsible for the death of the tubercle bacilli inside the lesion. On the other hand, in more recent lesions with open bronchi and relatively good blood supply, other factors, such as the drugs, must be considered. From these studies it is evident that continued investigation, correlating the pathologic and bacteriologic findings, is needed in order to determine the relative roles of natural healing and antimicrobial therapy with regard to the viability of the tubercle bacillus.

SUMMARY

A report of bacteriologic study for tubercle bacilli of 50 surgical specimens from 28 patients is presented.

The specimens are considered in three groups according to preoperative management. The first group had continuous streptomycin–para-aminosalicylic acid (PAS) therapy prior to surgery; the second had several courses of drug before surgery; and the third had no drug treatment.

The findings indicate that non-culturable tubercle bacilli were found in some cases in all of the groups.

The need for further correlative studies of the pathologic and bacteriologic findings of both untreated and treated tuberculous lesions is demonstrated.

SUMARIO

Estudio del Bacilo Tuberculoso en las Lesiones Pulmonares Resecadas

Este estudio bacteriológico de bacilos tuberculosos comprende 50 ejemplares quirúrgicos procedentes de 28 enfermos.

Los ejemplares fueron estudiados en tres grupos establecidos conforme a la asistencia preoperatoria. El primer grupo había recibido continuamente estreptomicina y ácido para-aminosalicílico antes de la cirugía; el segundo grupo había recibido varias tandas de medicación antes de la cirugía; y el tercero no había recibido medicación.

Los hallazgos indican presencia de bacilos tuberculosos no viables en algunos casos en todos los grupos.

Queda demostrada la necesidad de llevar a cabo más estudios correlacionados de los hallazgos patológicos y bacteriológicos en lesiones tuberculosas tanto tratadas como no tratadas.

RESUME

Une étude du bacille tuberculeux dans les tissus de lésions pulmonaires réséquées

Présentation d'un rapport bactériologique relatif à la recherche du bacille tuberculeux dans 94 pièces provenant de résections effectuées chez 28 malades.

Les spécimens ont été répartis en trois groupes, selon les divers traitements pré-opératoires. Le premier groupe représentait la catégorie du traitement continu pré-opératoire avec la streptomycine et l'acide para-aminosalicylique; le second la catégorie où quelques séries de traitement avaient été effectuées avant l'intervention; la troisième représentait l'absence de cette médication.

Les résultats montrent que des bacilles tuberculeux non-viables ont été découverts dans quelques cas et dans chacun des trois groupes.

Les auteurs montrent la nécessité de procéder à de nouvelles études sur les lésions tuberculeuses traitées et non traitées, où les données pathologiques et bactériologiques seraient confrontées.

Addendum

Since the present paper was submitted, the writers have had the opportunity to study operative specimens from 2 patients who have not had preoperative chemotherapy. The specimen from one of these patients was negative for acid-fast bacilli microscopically and by culture and guinea pig inoculation. Three specimens from the other patient were examined, one of which showed two acid-fast bacilli microscopically, but all of the three specimens were negative by culture and guinea pig inoculation.

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THE EFFECT OF ARTIFICIAL PNEUMOPERITONEUM ON THE BALLISTOCARDIOGRAPH OF PATIENTS WITH CHRONIC PULMONARY DISEASE[1, 2]

ANTHONY CACCESE

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INTRODUCTION

In routine ballistocardiograms on patients without demonstrable heart disease, it was noted that many patients with chronic pulmonary disease had unusually great variation in I-J amplitude during the respiratory cycle. Brown and associates (1) recently demonstrated that the increase in respiratory variation usually seen in patients with angina could be improved to within normal limits in 15 per cent of the cases by use of an abdominal belt. Since some of the present writer's patients with bilateral pulmonary tuberculosis and chronic pulmonary emphysema were to be treated with pneumoperitoneum, the effect of this procedure on the ballistocardiographic pattern was recorded.

METHOD

Simultaneous electrocardiograms (one lead) and electromagnetic ballistocardiograms (2) were recorded as control tracings during normal breathing and during held inspiration. The patient was then fitted with an elastic abdominal binder and the tracings repeated. Pneumoperitoneum was then induced by the Tuberculosis Service, Kings County Hospital. After the patient had a satisfactory pneumoperitoneum, the ballistocardiogram, with simultaneous electrocardiogram, was repeated.

A group of 9 patients was studied. Of these, 6 had bilateral pulmonary tuberculosis and 3 had chronic pulmonary emphysema.

RESULTS

Of the 6 patients with pulmonary tuberculosis, 5 had control ballistocardiograms with significant respiratory variation, and in 2 of these there was some distortion of the ballistocardiographic complexes. In 3 of the 6 patients, a decided improvement of the ballistocardiogram was observed after pneumoperitoneum. In only one of the 3 in whom marked improvement occurred had the abdominal binder been as effective as pneumoperitoneum in improving the ballistocardiogram (figure 1). In the remaining 3 patients with pulmonary tuberculosis, only slight improvement in the ballistocardiogram occurred as a result of the pneumoperitoneum, and in one case the belt was as effective as pneumoperitoneum.

[1] From the Department of Medicine, State University of New York, College of Medicine, New York City.

[2] This investigation was supported by a research grant from the National Institutes of Health, Public Health Service.

In the control tracings of the cases of chronic pulmonary emphysema, there was distortion of the ballistocardiographic complexes as well as an increase in respiratory variation. One of the 3 patients had a marked improvement of his ballistocardiogram after pneumoperitoneum, but not after the abdominal binder (figure 2). In one patient there was only slight improvement in the post-pneumoperitoneum normal breathing record, but significant improvement was noted in

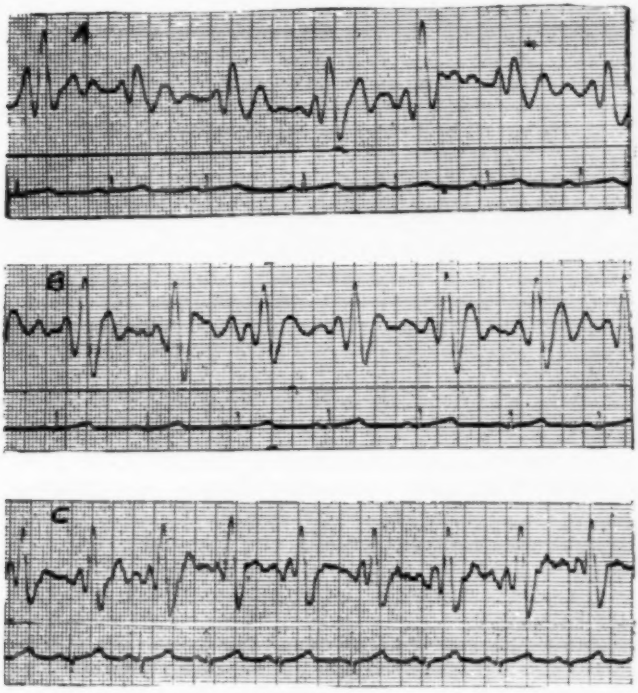

FIG. 1. The effect of an abdominal binder and of pneumoperitoneum on a 32-year-old patient with bilateral pulmonary tuberculosis. A. Control; note the marked degree of respiratory variation. B. After abdominal belt. C. After pneumoperitoneum. Marked improvement in respiratory variation noted after the belt and pneumoperitoneum.

the record taken during held inspiration after pneumoperitoneum. The third patient showed no improvement with the belt or pneumoperitoneum. The data from the 9 cases, showing the I-J amplitudes measured before and after treatment are summarized in table 1.

One patient with bilateral pulmonary tuberculosis (case not included in the above series) went into shock at the onset of pneumoperitoneum. It is of interest to note that the ballistocardiogram of this patient was made worse by the use of the abdominal binder.

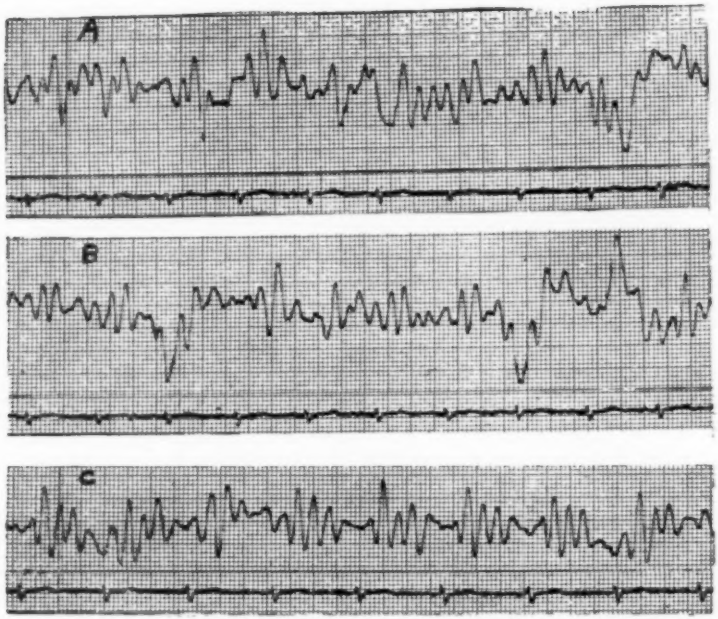

FIG. 2. The effect of an abdominal binder and of pneumoperitoneum on a 54-year-old patient with far advanced pulmonary emphysema. A. Control; note the respiratory variation and the distortion of most ballistocardiographic complexes. B. After abdominal belt. C. After pneumoperitoneum. Note the marked improvement in the ballistocardiographic complexes after pneumoperitoneum but little or none after the abdominal belt.

DISCUSSION

Study of this small series of cases indicates that the belt described by Brown, apparently one of the best yet designed for improving respiration in patients with abdominal relaxation, is not as effective as pneumoperitoneum in correcting the defect leading to an unusually wide respiratory fluctuation in the ballistocardiogram.

At least three factors seem to be involved in the great respiratory variation in I-J amplitude. One, which might be called "sensitivity of the right ventricle to priming" occurs after myocardial injury even in those who have no pulmonary disease and whose only peripheral vascular disorder would seem to be reflex disturbances following myocardial damage. This phenomena occurs in the purest form after myocardial infarction in young men.

Since the change in I-J seems to be due to the increase and decrease in right ventricular stroke volume, the important factor is the change in venous return to the right auricle, and not the volume of blood pooled in the pulmonary veins. The latter influences left ventricular output, and this increases in expiration,

TABLE 1

BALLISTOCARDIOGRAPHIC FINDINGS BEFORE AND AFTER THERAPY

SUBJECTS	NORMAL BREATHING (CONTROL)		NORMAL BREATHING WITH ABDOMINAL BELT		NORMAL BREATHING AFTER PNEUMOPERITONEUM		COMMENTS
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	
D. L. (Pulmonary tuberculosis)	21.3	9.2	17.7	13.7	16.3	13.2	Marked improvement in respiratory variation after belt and pneumoperitoneum
B. J. (Pulmonary tuberculosis)	20.0	9.0	14.0	8.3	8.7	6.5	A reduction in respiratory variation after both belt and pneumoperitoneum, more striking after pneumoperitoneum
M. J. (Pulmonary tuberculosis)	18.7	8.0	17.0	6.0	12.0	7.0	Marked improvement in respiratory variation and in the form of the ballistocardiographic complexes after pneumoperitoneum; the form of the complexes were made worse after belt
Mu.J. (Pulmonary tuberculosis)	19.0	7.7	15.0	6.7	18.0	8.0	No improvement in respiratory variation but a marked improvement in the form of the ballistocardiographic complexes after pneumoperitoneum
S. M. (Pulmonary tuberculosis)	20.5	11.0	16.0	12.1	14.3	10.0	Improvement in respiratory variation after belt and pneumoperitoneum
J. L. (Pulmonary tuberculosis)	15.0	9.6	9.0	7.0	12.0	9.0	Ballistocardiograph was normal in the control
N. R. (Pulmonary emphysema)	14.7	6.5	14.6	7.0	14.3	10.8	Marked improvement in respiratory variation and appearance of complexes after pneumoperitoneum
S. G. (Pulmonary emphysema)	15.0	7.5	18.9	9.0	19.6	12.6	Slight improvement in respiratory variation, and marked improvement in the form of the complexes in held inspiration after pneumoperitoneum
B. L. (Pulmonary emphysema)	21.0	9.0	26.0	8.0	20.0	8.0	No improvement following belt or pneumoperitoneum

The above figures represent an average height in mm. of the largest I-J waves in inspiration (maximum) and an average of the smallest I-J waves in expiration (minimum) recorded before and after treatment.

while the right ventricular output and the ballistic waves decrease. In chronic diseases of the lung, high intrathoracic pressure during expiration and fall in intra-abdominal pressure as the diaphragm rises will greatly reduce the gradient

between the abdominal venous pool and the right auricle and ventricle. On inspiration this is reversed more markedly than in normals, thus greatly increasing venous return. The third factor, elevated and labile intrapulmonic vascular resistance, would be of importance in modifying right ventricular output, regardless of the volume of blood in the pulmonic venous bed, or pulmonary pool.

The third factor, elevated and labile intrapulmonic vascular resistance, would be of importance in modifying right ventricular output, regardless of the volume of blood in the pulmonic venous bed or pulmonary pool.

Employing the cardiac catheterization technique, various investigators have reported an increase in intrapulmonary pressure in chronic pulmonary disease (3, 4, 5). Anoxia has been known to result in an elevation of the pressure in the pulmonary artery. Recently Westcott and co-workers (6) demonstrated that anoxia caused a prompt increase in the pulmonary vascular resistance, and discussed its probable contribution to pulmonary hypertension of chronic lung disease. It is believed (3) that, although reduction in the expansibility or distensibility of the vascular bed as a result of direct anatomic alteration may be a factor in producing an increase in pulmonary arterial pressure, the important cause of pulmonary hypertension in chronic pulmonary emphysema is the decrease in oxygen saturation of alveolar air.

In the cases in the present report, both pulmonic arterial resistance and the relative degree of pooling in the abdomen and in the thoracic venous reservoir would be altered by disease of the lungs and restored toward normal by raising intra-abdominal pressure and the level of the diaphragm. In cor pulmonale, effects on the heart itself also might be present. Pneumoperitoneum, by raising the diaphragm, has been shown to improve the various pulmonary function tests (7, 8, 9) and the degree of oxygen saturation (8, 9) and should reduce pulmonic vascular resistance. Raising intra-abdominal pressure undoubtedly reduces venous pooling there and increases the volume of blood in the thoracic venous reservoir.

SUMMARY

The increase in respiratory variation in amplitude of the ballistocardiogram, noted in cases of chronic pulmonary disease (chronic pulmonary emphysema and bilateral pulmonary tuberculosis), can in some cases be corrected by pneumoperitoneum. As a rule the improvement is greater than can be demonstrated to occur from a satisfactory elastic abdominal girdle.

The reduction of the respiratory ballistocardiographic variation by pneumoperitoneum is probably due, in part, to better ventilation, reduced anoxia, and fall in pulmonic arterial resistance; and to a reduction of abdominal pooling and an increased pooling in the preventricular intrathoracic venous reservoir.

SUMARIO

El Efecto del Neumoperitoneo Terapéutico sobre la Ballistocardiografía en los Enfermos con Afección Pulmonar Crónica

La hipervariación respiratoria traducida en emplitud del ballistocardiograma, que se observa en casos de afección pulmonar crónica (enfisema pulmonar y tuberculosis pulmonar

bilateral), puede ser rectificada en algunos casos con el neumoperitoneo. Por regla general, el mejoramiento es mayor que el que puede observarse con el empleo de una faja abdominal elástica satisfactoria.

La disminución ballistocardiográfica de la variación respiratoria obtenida por el neumoperitoneo se debe probablemente, en parte, a mejor ventilación, menos anoxia y baja de la resistencia arteriopulmonar; y a disminución del estancamiento abdominal con mayor estancamiento en el depósito venoso intratorácico preventricular.

RESUME

L'effet du pneumopéritoine artificiel sur le ballistocardiogramme de malades atteints d'affections pulmonaires chroniques

L'augmentation des différences d'amplitude observée dans le ballistocardiogramme des malades atteints d'affections chroniques du poumon (emphysème pulmonaire chronique et tuberculose pulmonaire bilatérale) peut parfois être corrigée par le pneumopéritoine. D'une manière générale, l'amélioration obtenue par ce procédé est supérieure à celle que donne le port d'une ceinture abdominale élastique convenable.

Il est probable que la diminution de la variation ballistographique respiratoire, déterminée par le pneumopéritoine, est due, en partie, à l'amélioration de la ventilation, à la réduction de l'anoxie et à l'abaissement de la résistance artérielle qui se produit au niveau du poumon, ainsi qu'à la réduction de la congestion veineuse abdominale et à une augmentation de la masse sanguine dans le réservoir préventriculaire intrathoracique.

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HEMAGGLUTINATION REACTION FOLLOWING BCG VACCINATION IN HUMAN SUBJECTS[1, 2]

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INTRODUCTION

In 1948, Middlebrook and Dubos (1) described a method for detecting the presence in serum of antibodies to certain antigenic components of *M. tuberculosis*. In this paper and in some reports that soon followed (2, 3), hope was entertained that this reaction would be of value as a diagnostic tool or as an index of activity of disease in patients known to have tuberculosis. More recent studies (4, 5, 6) have cast serious doubt on the validity of the hemagglutination reaction as a diagnostic procedure, since considerable numbers of both false-positive and false-negative reactions occur with the antigen now available. Without question, the range of titers found in the serum of normal individuals is nearly identical with that of patients with active tuberculosis. Nevertheless, a greater percentage of hemagglutinin titers in the range of 1:8 or above is encountered in tuberculosis patients, and the mean titer is significantly higher in this latter group (6). On this basis, there is general agreement that the test does measure an antibody present in many patients with active tuberculosis.

Up to the present, publications on this subject have been largely concerned with its possible clinical application, and data on the test following BCG vaccination in human subjects are meager. The present report deals with the behavior of the hemagglutination reaction in 166 normal young adults who received BCG vaccination.

MATERIALS AND METHODS

In the fall of 1950, a total of 191 entering student nurses and freshman medical students received BCG vaccination at the University of Michigan. Of these, 25 were lost to observation, leaving 166 subjects in whom the subsequent behavior of the hemagglutination titers could be followed. Each of the students who received BCG had been found to be negative to 1.0 mg. of Old Tuberculin, and a chest roentgenogram of each was normal.

Control serum specimens were obtained just prior to the initial tuberculin testing, and BCG vaccination was performed promptly, using the multiple-puncture disc method of Rosenthal. Serum specimens and tuberculin testing (1.0 mg. O.T.) were repeated at three months and again at seven months following vaccination. In each instance serum was obtained just before the tuberculin testing was done. Sera were frozen and maintained in this state until the hemagglutination tests were run.

The procedures for performance of the hemagglutination test which were used in this

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study were similar to those used in previous reports (1, 2, 3) except that human type "O" erythrocytes were used in place of sheep cells. The justification for the use of human erythrocytes, as well as precise details of technique, has been presented in a previous report (6) and will not be repeated here. The antigen used to sensitize the erythrocytes was a concentrated preparation of Old Tuberculin.[4] Tests were reproducible within the limits of one tube variation.

RESULTS

Hemagglutination titers in the control sera ranged from 0 to 1:64, with a positive reaction in dilution of 1:2 or greater present in approximately 50 per cent of the specimens. Following BCG vaccination, the behavior of the titers was often erratic in individual subjects, particularly among those in whom the control titer had been high. When the group as a whole was considered, however, there was a statistically significant shift toward higher titers among the specimens obtained three months following BCG vaccination.

TABLE 1

DISTRIBUTION OF HEMAGGLUTINATION TITERS IN 166 SUBJECTS BEFORE BCG VACCINATION AND AT THREE AND SEVEN MONTHS AFTER VACCINATION

SPECIMENS	TITERS								
	0	1:2	1:4	1:8	1:16	1:32	1:64	1:128	Total
Control	84	31	33	8	7	2	1		166
Three months after BCG	60	35	30	32	4	3	1	1	166
Seven months after BCG	84	34	32	7	7	2			166

Chi-square test of significance of difference between control and three-month values = 20.102, d.f. = 5, and $0.01 > P > 0.001$.

In table 1 may be seen the distribution of titers among the 166 subjects at each of the three determinations. The significant shift toward higher titers, which occurred three months after vaccination, was largely manifest by a reduction in the numbers showing no hemagglutination and an increase in the numbers at the 1:8 level. At seven months after BCG vaccination, the distribution had returned to one nearly identical to the control. These same data are presented graphically in figure 1. The mean titer,[5] which is one method of expressing the average amount of antibody in a given group of sera, showed comparable changes rising from a control value of 3 to 4.8 at three months and returning to 2.5 at seven months after BCG vaccination.

Complete data on the tuberculin reaction were available for 156 subjects. In this group there was no correlation between the rise in mean titer and the behavior of cutaneous sensitivity to tuberculin. This is illustrated in figure 2.

[4] Lederle four times standard strength Old Tuberculin, provided through the courtesy of Dr. H. D. Piersma.

[5] If it is assumed that it requires one unit of agglutinating antibody to produce a positive reaction in this test, then a serum giving agglutination in dilution of 1:64 would contain 64 such units. The sum of such units within a given group of sera divided by the number of specimens gives the mean titer.

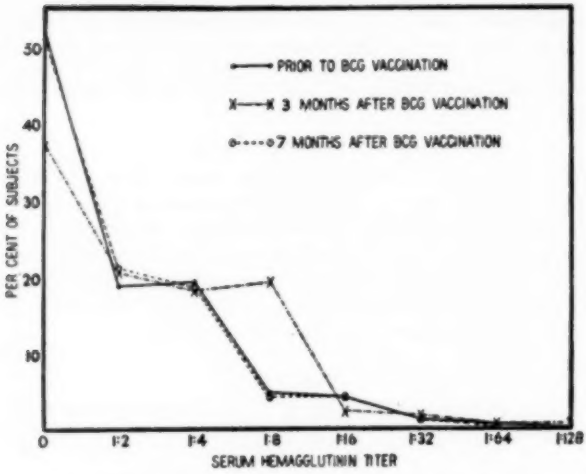

FIG. 1. Percentage distribution of hemagglutination titers in 166 subjects before BCG vaccination and at three and seven months thereafter.

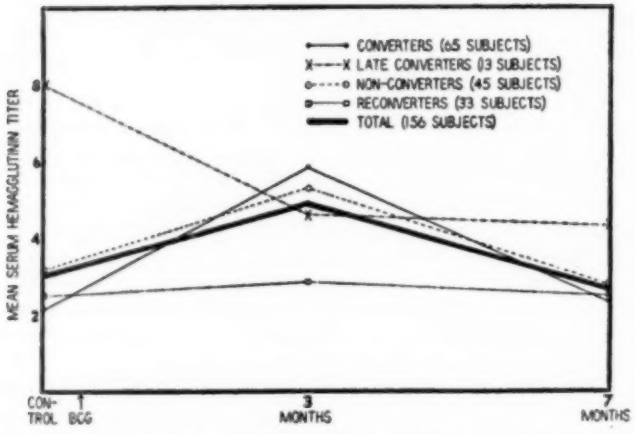

FIG. 2. Lack of correlation between the mean titer and the cutaneous reaction to tuberculin following BCG vaccination in 156 subjects. Subjects are classified according to cutaneous reaction to 1.0 mg. of Old Tuberculin:

"Converters": + at three months, + at seven months
"Late converters": − at three months, + at seven months
"Non-converters": − at three months, − at seven months
"Reconverters": + at three months, − at seven months

The changes in mean titer were similar in magnitude for the 65 subjects who became and remained positive to tuberculin and for the 45 subjects who failed to convert to positive during the seven months of observation. The erratic behavior of the mean titer in the remaining two categories can probably be best explained on the basis of the small numbers involved.

COMMENT

The appraisal of the antibody response to BCG vaccination in this group of subjects was hampered to a considerable extent by the fact that approximately 50 per cent of the control sera showed some degree of hemagglutination. Changes in the level of these nonspecific reactions, which ranged as high as 1:64, undoubtedly accounted for the erratic behavior of subsequent hemagglutination titers in individual cases. Nevertheless, when the whole group is considered, the significant shift toward higher titers, which occurred at three months, and the return to control values at seven months after vaccination offers convincing evidence that a new and specific antibody had been present.

The significance of the specific antibody responsible for the hemagglutination reaction is unknown except for the fact that it is most prominent in patients with advanced, active disease. Whether it plays any useful role in the immune processes is certainly open to question, although it is reasonable to assume that it is not entirely dissociated from such mechanisms. In view of this, it is disappointing that the response to BCG was so meager and transient. It is of some interest, however, that such response as could be demonstrated bore no relationship to the development of tuberculin sensitivity.

SUMMARY

With the use of the Middlebrook hemagglutination technique, it has been possible to demonstrate an antibody response to BCG vaccination in a group of 166 subjects. This antibody response was quantitatively of very low order, was transient, and bore no relation to the development of cutaneous hypersensitivity to tuberculin.

SUMARIO

La Hemaglutinorreacción de Middlebrook para la Tuberculosis Consecutiva a la Vacunación con BCG en Sujetos Humanos

Usando la técnica de la hemaglutinación de Middlebrook, fué posible descubrir una reacción en anticuerpos a la vacunación con BCG en un grupo de 166 sujetos. Esa reacción de anticuerpos fué cuantitativamente muy baja, y además pasajera, sin guardar la menor relación con la sensibilidad a la tuberculina.

RESUME

Le test d'hémagglutination de Middlebrook dans la tuberculose consécutive à la vaccination par le BCG chez l'homme

L'utilisation du procédé d'hémagglutination de Middlebrook a permis de démontrer la production d'anticorps en réponse à la vaccination par le BCG, dans un groupe de 166 sujets. Cette production d'anticorps était quantitativement de faible degré, elle était transitoire et sans relation avec la sensibilité à la tuberculine.

Acknowledgment

The authors are indebted to Dr. James V. Neel for statistical evaluation of the material contained in table 1. Miss Kathryn Miller gave valuable technical assistance.

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THE OCCURRENCE OF TUBERCLE BACILLI RESISTANT TO STREPTOMYCIN IN CHILDREN WITH TUBERCULOSIS[1,2]

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INTRODUCTION

As part of a study of the chemotherapy of tuberculosis in children, cultures of *M. tuberculosis* obtained from patients in the tuberculosis ward of the Children's Medical Service of Bellevue Hospital have been tested for sensitivity to streptomycin *in vitro* whenever the necessary subcultures could be obtained. During the last two years the number of such sensitivity tests has closely approximated the total number of positive cultures. It is the purpose of this paper to report the results of the sensitivity tests in the 152 patients tested, and to discuss the occurrence or emergence of resistance in the patients with tubercle bacilli resistant to 10 or more γ of streptomycin per ml. All of the patients in this series were less than thirteen years of age.

METHOD OF STUDY

Source of Material

The material used for culture was obtained from gastric washings, bronchial secretions obtained by aspiration during bronchoscopy, cerebrospinal fluid, sputum, pleural fluid, urine, whole blood, biopsy or aspiration of lymph nodes, stools, adenoid tissue, and material from the middle ear.

Method of Culture

Preparation: The gastric washings, urine, and bronchial secretions were treated by concentration and digestion with 3 per cent sodium hydroxide followed by neutralization with 3 per cent sulfuric acid, using thymol blue as an indicator. Urine specimens were treated with 5 per cent tannic acid before digestion and concentration and represented twenty-four-hour urine collections when possible. During the last year, cerebrospinal fluids obtained on two or three consecutive days were pooled.

Culture procedure: The material to be cultured was inoculated into plates of solid Dubos medium containing 50 units per cc. of penicillin and into Petragnani slants. The cerebrospinal fluid was poured directly over the surface of a slant of Petragnani medium and a plate of Dubos medium. The cultures were examined weekly and smears were made. Usually three to six weeks were required for growth. If no growth was observed after eight weeks, the cultures were discarded.

Determination of Sensitivity of Tubercle Bacillus to Streptomycin

A ten- to twelve-day-old subculture growing in Dubos liquid medium of the organism which was originally isolated in Petragnani or Dubos solid medium was used for the test.

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[2] This study was aided by grants from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association; from Parke, Davis and Company; and from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service.

In many instances the test culture was taken from a single colony; in others it represented a streak through a number of colonies. A series of tubes was set up containing 5 ml. of liquid Dubos medium with 1, 2, 5, 10, and 100 γ of streptomycin per ml. and a control tube without streptomycin. In some instances other concentrations of streptomycin were used; the series did not include a tube containing 1,000 γ of streptomycin per ml. as a routine. The tubes were inoculated with 0.1 ml. of the culture diluted to contain approximately

TABLE 1

TOTAL NUMBER OF CULTURES POSITIVE FOR M. TUBERCULOSIS OBTAINED AND TOTAL NUMBER OF CULTURES WITH TUBERCLE BACILLI TESTED FOR DRUG SENSITIVITY, ACCORDING TO DIAGNOSIS OF PATIENTS

DIAGNOSIS	NUMBER POSITIVE		NUMBER TESTED FOR DRUG SENSITIVITY OF ORGANISMS	
	Patients	Cultures	Patients	Cultures
Acute meningitis	14	45	10	27
Acute meningitis with miliary tuberculosis	11	47	8	24
Chronic meningitis with miliary tuberculosis (A)	1	32	1	26
Miliary tuberculosis	7	37	6	25
Progressive primary tuberculosis (B)	19	75	17	53
Moderately or far advanced chronic pulmonary tuberculosis	18	89	16	55
Other diagnoses (C)	123	257	94	177
Totals	193	582	152	387

(A) Case J. O'R.

(B) Defined as local progression of primary focus with cavitation and bronchogenic spread.

(C) Includes primary tuberculosis, endobronchial tuberculosis, minimal chronic pulmonary tuberculosis, tuberculosis of bone, et cetera.

one million organisms per milliliter determined by comparing turbidity with a nepholometer. The tubes were set up as follows:

Tube	*1*	*2*	*3*	*4*	*5*	*6*	
Streptomycin, γ per ml.	100	10	5	2	1	0	
Growth at one week	0	0	0	+	+	+	
Growth at two weeks	0	0	0	++	++	++	et cetera

The tubes were inspected at weekly intervals, with a final determination after two weeks. The absence of growth in any tube was taken as an indication of the sensitivity of the organisms to streptomycin.

RESULTS

During the four-year period of the study (December, 1946, to April, 1951), 582 cultures of tubercle bacilli from various sources were obtained from 193 patients. Tubercle bacilli obtained from 387 cultures, representing 152 patients, were tested for the sensitivity of the organisms to streptomycin. In table 1 is shown the relation between the total number of positive cultures obtained and the patients whose organisms were tested for sensitivity to streptomycin, according to the tuberculous lesions of the patients.

Of the 387 cultures of tubercle bacilli which were tested for sensitivity to streptomycin, 187 were obtained from 115 patients not previously treated with streptomycin, and 200 cultures were obtained from 59 patients during and after streptomycin therapy (table 2). Cultures from 22 of these 59 patients had been tested for the sensitivity to streptomycin before therapy was begun and are included in the 115 patients noted above.

Forty-six of the 387 cultures tested yielded organisms resistant to at least 10 γ of streptomycin per ml. These 46 cultures were obtained from 17 patients. Seven cultures obtained from 5 patients not previously treated with streptomycin contained tubercle bacilli resistant to 10 γ or more of streptomycin per ml. Thirty-nine cultures obtained from 13 patients during or after treatment

TABLE 2

NUMBER OF PATIENTS AND CULTURES WITH TUBERCLE BACILLI TESTED FOR SENSITIVITY TO STREPTOMYCIN IN RELATION TO TREATMENT

	NUMBER OF PATIENTS	NUMBER OF CULTURES
Not previously treated with streptomycin	115	187
During or after treatment with streptomycin	59	200

TABLE 3

NUMBER OF PATIENTS AND CULTURES WITH TUBERCLE BACILLI SENSITIVE OR RESISTANT TO 10 γ OF STREPTOMYCIN PER ML.

	NOT PREVIOUSLY TREATED WITH STREPTOMYCIN			DURING OR AFTER TREATMENT WITH STREPTOMYCIN		
	Number Sensitive to 10 γ per ml.	Number Resistant to 10 γ per ml.	Total	Number Sensitive to 10 γ per ml.	Number Resistant to 10 γ per ml.	Total
Patients	110	5*	115	46	13*	59
Cultures	180	7	187	161	39	200

* Total, 17 patients, includes a patient whose organisms were resistant before and during treatment with streptomycin.

with streptomycin showed organisms resistant to at least 10 γ of streptomycin per ml. The number of patients and cultures with organisms sensitive or resistant to 10 γ per ml. are noted in table 3. One patient had organisms resistant to streptomycin before and during treatment and is included under both headings.

All but 20 of the patients (24 of the cultures) reported in table 3 to have organisms sensitive to 10 γ of streptomycin per ml. had organisms sensitive to 1.0 to 2.5 γ of streptomycin per ml. Seven of the group of 20 patients had organisms resistant to 5 γ per ml. and sensitive to 10 γ of streptomycin per ml. The organisms of 12 patients were not tested for sensitivity at levels between 1 and 10 γ of streptomycin per ml.; these organisms were resistant to 1 γ per ml. and sensitive to 10 γ of streptomycin per ml. Gastric washings of one patient contained organisms resistant to 5 γ per ml. but sensitive to 10 γ per ml. before treatment with streptomycin. A culture obtained after one month of strepto-

mycin contained organisms which showed plus-minus resistance to 10 γ but which were sensitive to 100 γ of streptomycin per ml. The organisms of this patient have been regarded as sensitive to 10 γ per ml. for the purpose of this study.

TABLE 4

NATURE OF LESION IN PATIENTS WITH TUBERCLE BACILLI RESISTANT TO 10 γ OF STREPTOMYCIN PER MILLILITER IN RELATION TO DURATION OF STREPTOMYCIN THERAPY

	DURATION							
	No Therapy	2 Weeks	5 Weeks	11 Weeks	17 Weeks	23 Weeks	6 Months or More	Number of Cultures
Tuberculous meningitis								
Patients	—	—	—	—	—	—	2	
Cultures	—	—	—	—	—	—	2	2
Acute meningitis with miliary tuberculosis								
Patients	—	—	—	—	—	—	2	
Cultures	—	—	—	—	—	—	2	2
Chronic meningitis with miliary tuberculosis (A)								
Patients	—	—	—	—	—	—	1	
Cultures	—	—	—	—	—	—	18	18
Miliary tuberculosis								
Patients	1	—	—	—	1	2	—	
Cultures	1	—	—	—	2	5	—	8
Progressive primary tuberculosis								
Patients (B)	—	—	—	3	—	—	—	
Cultures	—	—	—	3	—	—	—	3
Moderately or far advanced chronic pulmonary tuberculosis								
Patients	1	—	—	1	1	1	—	
Cultures	3	—	—	2	3	2	—	10
Other diagnoses (C)								
Patients	3	—	—	—	—	—	—	
Cultures	3	—	—	—	—	—	—	3
Total								46

(A) Case J. O'R.

(B) Defined as local progression of primary focus with cavitation and bronchogenic spread.

(C) Includes primary tuberculosis, endobronchial tuberculosis, minimal chronic pulmonary tuberculosis, tuberculosis of bone, et cetera.

Further observations on the 17 patients and their 46 cultures containing organisms resistant to 10 γ of streptomycin per ml. follow.

Duration of streptomycin therapy: The duration of streptomycin therapy at the time resistant cultures were found is tabulated in relation to the diagnoses of the 17 patients with organisms resistant to 10 γ of streptomycin per ml. (table 4).

Sources of drug-resistant M. tuberculosis: The sources of the culture material are given in table 5. The number of cultures from each source containing organisms resistant to 10 γ of streptomycin per ml. is compared with the number of cultures from each source containing organisms sensitive to 10 γ of streptomycin per ml.

Degree of drug resistance: The degree of resistance exhibited by the organisms tested for sensitivity varied in individual patients. Only one (J. Y.) of the 17 patients had organisms known to be resistant to 1,000 γ of streptomycin per ml., 10 patients had organisms known to be resistant to 100 γ of streptomycin per ml. Of these 10 patients, one had organisms resistant to 100 γ but sensitive to 1,000 γ of streptomycin per ml.; the other 9 had organisms whose sensitivity was not further tested. Three patients had organisms resistant to 10 γ but sensitive to 100 γ of streptomycin per ml.; the remaining 3 (of the 17 patients) had organisms

TABLE 5

SOURCES OF CULTURES CONTAINING TUBERCLE BACILLI SENSITIVE OR RESISTANT TO 10 γ OF STREPTOMYCIN PER MILLILITER

SOURCE	NUMBER OF CULTURES	
	Sensitive to 10 γ per ml.	Resistant to 10 γ per ml.
Gastric washings	235	19
Bronchial secretion	36	5
Cerebrospinal fluid	46	21
Pleural fluid	1	1
Sputum	6	—
Ear	6	—
Lymph node	8	—
Stool	1	—
Adenoids	1	—

resistant to 10 γ and sensitive to 25 γ of streptomycin per ml. The sources of cultures with resistant organisms are related to the degree of resistance in table 6.

Pattern of the appearance of drug-resistant M. tuberculosis: The inconstancy of occurrence of resistance is best illustrated in the short case histories which follow. It should be noted that 11 of the 17 patients had only one culture which contained organisms resistant to 10 γ or more of streptomycin per ml., while 2 patients had 2 cultures each with resistant organisms and 2 patients had 3 cultures each. The remaining 2 patients had 7 and 18 cultures with resistant organisms, respectively (T. B. and J. O'R.). The inconstancy in the occurrence of resistance and the variability in degree of resistance are of significance only in relation to the clinical course of the patients. Two patients showed inconstancy in the occurrence of resistance before treatment and 6 patients showed variation during treatment. Only one of the latter had organisms predominantly resistant to 100 γ of streptomycin per ml.

From the clinical standpoint, the 17 patients with organisms resistant to 10 γ

of streptomycin per ml. can be divided into two major groups. One group consists of patients in whom an obvious correlation exists between the laboratory and the clinical findings; the other, of those in whom the correlation cannot be made at the present time. The latter group can be subdivided into (*1*) patients who had organisms resistant to 10 γ of streptomycin per ml. before treatment was given, (*2*) patients who had a culture with resistant organisms followed by a culture with sensitive organisms, and (*3*) patients whose last positive culture tested for sensitivity contained resistant organisms.

TABLE 6

RELATION OF DEGREE OF DRUG RESISTANCE TO SOURCE OF CULTURE

DEGREE OF DRUG RESISTANCE	GASTRIC WASHING	BRONCHIAL SECRETION	CEREBROSPINAL FLUID	PLEURAL FLUID
Resistant to 10 or more, sensitive to 100 γ per ml.	7	2	19	
Resistant to 100, sensitive to ? γ per ml.	12	3		1
Resistant to 100, sensitive to 1,000 γ per ml.			1	
Resistant to 1,000, sensitive to ? γ per ml.			1	

CASE HISTORIES

Positive Correlation Between Sensitivity Studies and Course

The patient, J. Y., had miliary tuberculosis followed by tuberculous meningitis and relapse of the meningitis. He was treated with streptomycin and Promizole for miliary tuberculosis and developed meningitis. Relapse occurred eighteen days after streptomycin was discontinued. Tubercle bacilli from the cerebrospinal fluid at the time of relapse were sensitive to 2.5 γ of streptomycin per ml. Two months later, just before the patient's illness started the downhill course which ended in his death, organisms obtained from the cerebrospinal fluid were resistant to 1,000 γ of streptomycin per ml.

The patient, J. O'R., had chronic meningitis and miliary tuberculosis. The meningitis had been diagnosed sixteen months prior to admission to Bellevue Hospital and had been treated with streptomycin for four and one-half months and with Promizole for approximately one year. Two months before admission to Bellevue, the patient developed miliary tuberculosis and was re-treated with dihydrostreptomycin and Promizole. On admission, relapse of the meningitis was also diagnosed. At this time the tubercle bacilli from the gastric washings were sensitive to 2.5 γ of streptomycin per ml. Treatment with dihydrostreptomycin and Promizole was continued until the patient's death six months later. Organisms from four cultures from the cerebrospinal fluid were sensitive to 6.2 γ of streptomycin per ml. As the patient's clinical condition deteriorated, the degree of resistance increased, first to 12.5 γ, then to 25 γ of streptomycin per ml. (number of colonies varied from one to many without relation to degree of resistance[2]), and in the next two months to 50 γ of streptomycin per ml. A final culture contained tubercle bacilli resistant to 100 γ and sensitive to 1,000 γ of streptomycin per ml. at the time of death, six months after treatment for the relapse of the meningitis was begun.

The patient, T. B., had miliary tuberculosis. This patient had been in direct contact with her father who was hospitalized with active pulmonary tuberculosis. No information could be obtained which might suggest that the father had ever been treated with

[2] The number of colonies present on the plate from which the test culture was taken is noted wherever known.

streptomycin. The first positive culture of gastric washings obtained at the beginning of treatment with streptomycin and Promizole contained tubercle bacilli resistant to 100 γ of streptomycin per ml. (1 colony). Subsequent positive cultures of gastric washings obtained two weeks and two months after the start of treatment contained bacilli sensitive to 10 γ of streptomycin per ml. Three to five months after the start of therapy, however, 6 cultures of tubercle bacilli from gastric washings were resistant to 100 γ of streptomycin per ml. (1 colony, 8 colonies, 4 colonies, 4 colonies, 10 colonies, and 8 colonies, respectively). A seventh positive culture from a bronchial aspiration contained bacilli sensitive to 10 γ of streptomycin per ml. five months after the start of therapy. Subsequently, a variation in resistance from 5.0 γ to 100 γ of streptomycin per ml. (more than 20 colonies) was noted in the next two positive cultures of gastric washings. The patient showed no improvement in her clinical condition until two months after the start of treatment when some effect from the Promizole might have been expected; there was no improvement as judged by chest roentgenogram until seven months after treatment was started, a time when response to Promizole, as judged by roentgenography, would be expected.

Lack of Correlation Between Sensitivity Studies and Present Course

Drug-Resistant M. Tuberculosis Present Before Treatment with Streptomycin Without History of Contact

The patient, S. P., had endobronchial tuberculosis. Before the start of treatment with streptomycin and Promizole, the cultures of gastric washings contained tubercle bacilli sensitive to 5.0 γ of streptomycin per ml.; at the same time cultures of a bronchial aspiration contained bacilli resistant to 10 γ and sensitive to 100 γ of streptomycin per ml. (3 colonies). No cultures of *M. tuberculosis* were obtained after the start of treatment. The patient has had a satisfactory clinical course.

The patient, P. P., had endobronchial tuberculosis. Cultures of gastric washings obtained before treatment with streptomycin and Promizole contained tubercle bacilli sensitive to 1.25 γ of streptomycin per ml.; cultures of bronchial aspirations also obtained before treatment was started were resistant to 100 γ of streptomycin per ml. The patient's course was uneventful, and there were no subsequent cultures positive for *M. tuberculosis*.

The patient, L. S., had pleurisy with effusion. On admission, a culture of pleural fluid contained tubercle bacilli resistant to 10 γ of streptomycin per ml. with plus-minus resistance to 100 γ of streptomycin per ml. (1 colony).

The patient, E. E., had moderately advanced chronic pulmonary tuberculosis. Tubercle bacilli resistant to 10 γ per ml. but sensitive to 100 γ of streptomycin per ml. were obtained from three gastric washings before treatment with streptomycin and para-aminosalicylic acid (PAS). The patient had no cultures positive for *M. tuberculosis* after the start of streptomycin therapy, and there was good response to treatment.

Drug-Resistant Tubercle Bacilli Present in a Single Culture, Followed by Cultures Containing Sensitive Organisms

The patient, B. P., had tuberculous meningitis, with relapse. Tubercle bacilli in cultures of the cerebrospinal fluid were sensitive to 2.5 γ and 1.0 γ of streptomycin per ml. after seven months, thirteen months, fifteen months, twenty-one months, twenty-seven months, and twenty-nine months of almost continuous treatment with streptomycin, given intramuscularly and intrathecally, and with Promizole administered by mouth. A single culture of cerebrospinal fluid contained tubercle bacilli resistant to 10 γ but sensitive to 25 γ of streptomycin per ml. after fourteen months of treatment. The child died in a third relapse of the illness, with tubercle bacilli in the cerebrospinal fluid sensitive to 1.0 γ of streptomycin per ml. at the time of death.

The patient, J. M., had progressive primary tuberculosis. Culture of gastric washings contained tubercle bacilli sensitive to 1.0 γ of streptomycin per ml. at the start of treatment. Organisms from a single gastric washing were resistant to 100 γ of streptomycin

per ml. after two months of treatment with streptomycin and Promizole. Subsequent late cultures of gastric washings, seven months after completion of the two months of therapy, contained tubercle bacilli sensitive to 1.25 and 2.0 γ of streptomycin per ml. The child's progress was excellent.

The patient, J. Ag., had progressive primary tuberculosis. Tubercle bacilli sensitive to 1.0 and 5.0 γ of streptomycin per ml. were obtained from cultures of gastric washings one week, three weeks, and one month after start of treatment with streptomycin and Promizole. A culture of bronchial aspirations contained bacilli resistant to 100 γ of streptomycin per ml. (more than 20 colonies) after two months of treatment; after three months of treatment, gastric washings contained tubercle bacilli sensitive to 5.0 γ of streptomycin per ml. An excellent response to treatment was obtained.

The patient, K. M., had far advanced chronic pulmonary tuberculosis. Tubercle bacilli obtained from sputum were sensitive to 15.6 γ of streptomycin per ml. before treatment. Three positive cultures of gastric washings contained organisms sensitive to 2.5 γ of streptomycin per ml. three to six months after four months of therapy with streptomycin had been completed. A culture of gastric washings obtained ten months after completion of the streptomycin therapy yielded tubercle bacilli resistant to 100 γ of streptomycin per ml. Three months later a culture from gastric washings contained bacilli resistant to 10 γ per ml. with plus-minus resistance to 100 γ of streptomycin per ml.; no further streptomycin had been given. Two sporadic cultures two years later contained tubercle bacilli sensitive to 1.0 γ and 6.2 γ of streptomycin per ml. Good response to further streptomycin, PAS, and pneumothorax was obtained in this patient.

Drug-Resistant Organisms Present in the Last Culture Tested for Streptomycin Sensitivity

The patient, M. M., had tuberculous meningitis with relapse. Culture of the cerebrospinal fluid contained tubercle bacilli sensitive at the start of the original course of treatment with intramuscular and intrathecal streptomycin and Promizole. At the onset of relapse, forty-three days after completion of six months of therapy, 2 cultures of the cerebrospinal fluid contained tubercle bacilli sensitive to 2.5 γ of streptomycin per ml. A culture of the cerebrospinal fluid, two days after starting treatment for relapse, contained bacilli resistant to 10 γ but sensitive to 25 γ of streptomycin per ml. A positive culture of the cerebrospinal fluid obtained fifty-three days later was not tested for drug susceptibility. The child is well two and a half years after completion of streptomycin therapy.

The patient, R. C., had tuberculous meningitis and miliary tuberculosis which were treated with streptomycin intramuscularly and intrathecally and with Promizole orally. Cultures of cerebrospinal fluid contained tubercle bacilli sensitive to 5.0, 1.0, and 2.5 γ of streptomycin per ml. after two weeks, three weeks, and three months of treatment. A culture of bronchial secretions, obtained fourteen months after the completion of seven months of therapy, contained tubercle bacilli resistant to 100 γ of streptomycin per ml. (1 colony). Another positive culture of bronchial secretions was obtained three months later but was not tested for drug susceptibility. The miliary lesions and the meningitis responded well to treatment and the child has remained well for three years.

The patient, M. Sp., had miliary tuberculosis which was treated originally with streptomycin and Promizole but later with PAS alone. The response to streptomycin was slow but satisfactory. Cultures of gastric washings contained tubercle bacilli sensitive to 2.5 γ of streptomycin per ml. (1 colony) in the first week and in the third month of treatment. Cultures of gastric washings obtained after a total of five months of streptomycin therapy contained tubercle bacilli sensitive to 5 γ of streptomycin per ml. two months and three months after the completion of streptomycin treatment, while a third gastric washing obtained seven months after completion of streptomycin treatment yielded bacilli with a one plus resistance to 5.0 γ and a plus-minus resistance to 10 and 100 γ of streptomycin per ml. At this time the patient was receiving only PAS. The child has remained well clinically, although a small cavity persists on the roentgenogram.

The patient, R. Mi., had progressive primary tuberculosis. Culture of a gastric wash-

ing one month after treatment with streptomycin and Promizole had been started contained tubercle bacilli sensitive to 1.0 γ of streptomycin per ml. One month later a culture of gastric washings contained bacilli resistant to 100 γ of streptomycin per ml. No subsequent cultures for tubercle bacilli were obtained, and the patient has continued to do well after the completion of therapy.

The patient, E. W., had far advanced pulmonary tuberculosis which was treated with streptomycin and PAS. Tubercle bacilli isolated from the patient at the onset of therapy were sensitive to 1.0 γ of streptomycin per ml. Cultures from 2 gastric washings obtained ten months after completion of two months of streptomycin therapy contained tubercle bacilli which were resistant to 10 γ and sensitive to 25 γ of streptomycin per ml. The patient developed tuberculous laryngitis at this time and was re-treated with streptomycin for three weeks with good response of the laryngitis, although the cavity persisted on the roentgenogram. She has remained well after an extrapleural thoracoplasty, and there have been no further cultures positive for *M. tuberculosis*.

The patient, R. K., had far advanced chronic pulmonary tuberculosis. Cultures of gastric washings contained tubercle bacilli sensitive to 1.25 γ of streptomycin per ml. at the beginning of treatment with streptomycin and Promizole. After one month of treatment, tubercle bacilli were obtained which were resistant to 5.0 γ but sensitive to 10 γ of streptomyin per ml. One month after the completion of the three-month course of therapy, a culture of tubercle bacilli was resistant to 25 γ but sensitive to 50 γ of streptomycin per ml. Subsequent cultures of gastric washings and bronchial aspirations five months after completion of streptomycin therapy, while the patient was still receiving Promizole, yielded tubercle bacilli resistant to 5.0 and 10 γ but sensitive to 100 γ of streptomycin per ml. The patient has continued to do well clinically.

DISCUSSION

The principal purpose in preparing the present report has been to present in some detail the actual experience with drug-sensitivity studies of tubercle bacilli obtained from a group of patients under thirteen years of age. As the study has progressed, it has been obvious that, although the principles governing the appearance of resistant organisms must be the same for patients of all ages, the pattern of emerging resistance may vary in different age groups.

There was no reason to think that streptomycin would not be equally effective in all age groups. The efficacy of streptomycin depends on the fact that most organisms found in cultures positive for tubercle bacilli are fully sensitive to streptomycin. Youmans and Karlson (1) reported that 90 per cent of the strains they studied were sensitive to 2.0 γ of streptomycin per ml. Unfortunately, the continued effective use of streptomycin has been found to be limited by the development of resistance to the drug. Barnwell, Bunn, and Walker (2) in 1947 reported the development of resistant organisms in the group of 237 patients treated by the Army, Navy, and Veterans Administration. They suggested that the presence of organisms resistant to 10 γ of streptomycin per ml. was clinically significant. Bernstein, D'Esopo, and Steenken (3) pointed out that this division was more than hypothetical, since with 1.0 gm. of streptomycin given daily in divided doses intramuscularly a plasma concentration of approximately 10 γ of streptomycin per ml. was maintained, and that a patient who did not respond to therapy on this regimen would probably prove to have tubercle bacilli resistant to 10 γ of streptomycin per ml. on culture. In accordance with these assumptions, in the present study, sensitivity to 10 γ of streptomycin per ml. was chosen as

the degree of sensitivity which divided "resistant" from "nonresistant" organisms. As previously noted, the presence of resistance to 2.5 γ of streptomycin per ml. occurred in the present series without relation to the subsequent emergence of any greater resistance. Moreover, no evidence was found in patients with organisms resistant to 10 γ of streptomycin per ml. that this resistance could be related to the previous existence of organisms resistant to 2.5 γ or 5.0 γ of streptomycin per ml. but not resistant to 10 γ of streptomycin per ml.

It has been repeatedly demonstrated that drug-resistant tubercle bacilli exist in cultures which have not previously been exposed to streptomycin. Ferebee and Appel (4) report that 13 of a group of 175 children studied were discharging tubercle bacilli resistant to streptomycin before treatment. The source of infection was not noted. Five of the 115 patients studied in the present series discharged tubercle bacilli which were resistant before treatment with streptomycin, indicating either the presence of naturally occurring drug-resistant organisms or infection from sources already exposed to and resistant to streptomycin as reported by Furtos and co-workers (5) and other investigators.

It has been suggested that, if the drug-resistant tubercle bacilli occur naturally, the appearance of resistant variants and their subsequent behavior is in accord with the general bacteriologic principles governing bacterial mutations. As far as the actual mechanism is concerned, Alexander and Leidy (6) have demonstrated that the desoxyribonucleic acid fractions of *H. influenzae* may function as genes and direct the inherited traits of this organism. By analogy, changes in the desoxyribonucleic acid systems or similar basic systems of a single tubercle bacillus may explain the occurrence of variants resistant to streptomycin. Yegian and Vanderlinde (7) point out that drug-resistant cultures have arisen from a single sensitive cell in certain bacteria other than *M. tuberculosis*.

The subsequent behavior of resistant variants has been observed by Youmans and Williston (8) who have noted that drug-resistant cultures of H37Rv remained resistant in serial cultures *in vitro*. This is of interest, as the variability in the drug resistance of tubercle bacilli reported in the present series suggests that organisms are being obtained from different sites in the lung as reported by other observers, or that the *in vitro* sensitivity studies are not representative of the sensitivity *in vivo*. This latter possibility seems particularly likely in view of the fact that some of the subcultures used in sensitivity studies in the present series were obtained from a single colony. Two different factors are introduced here: the use of a single colony may favor the artificial selection of a resistant colony, but the relatively few organisms found diminish the chance of obtaining variant resistant organisms.

Alexander and Leidy (9, 10), working with gram-negative bacilli, explained the emergence of resistance as a result of bacterial mutation giving rise to resistant variants which bred true. This phenomenon was more frequent when the bacterial colony was large. They also noted that the size of the inoculum was the most important single factor in determining the emergence of resistance, but showed that the ratio of drug-resistant organisms was no greater initially in patients who became resistant. Although their work was done with gram-nega-

tive bacilli, it may help to explain the mechanisms of streptomycin resistance in tuberculosis. Thus, the emergence of resistant mutants is established as a selective phenomenon, with greater chances of a significant number of resistant variants in a larger population in which, as the sensitive organisms die, resistant organisms breed true and multiply. The drug-resistant bacteria then represent an appreciable percentage of the culture and determine the clinical response of the patient. Thus, the size of the inoculum in determining the presence of a significant number of resistant organisms appeared to be important both *in vivo* and *in vitro* in the present series. The absence of large numbers of organisms in many of the forms of tuberculosis common in children should decrease the chances of the emergence of a "clinical resistance" to streptomycin which is also reflected in the *in vitro* studies.

Other factors in the laboratory determination of sensitivity may influence the results obtained. Youmans and Williston (8) repeated the work of Vennesland, Ebert, and Bloch (11) and found that the resistant organisms which emerged had a longer incubation period than the sensitive colonies and were fewer in number. The amount of growth and time of appearance of resistant organisms varied proportionately with the percentage of the total population of a culture. Thus, when only a few organisms are present, a final reading after two weeks may not allow sufficient time for the growth of resistant organisms. On the other hand, Wolinsky and Steenken (12) refer to the effect of changes in pH and to the effect of lengthening the incubation period on breaking through an "inhibitory factor" which results in the growth of sensitive organisms. Bernstein and associates (3) refer to the possibility that too large an inoculum increases the chances for a high rate of prevalence of resistant mutants and also point out that 0.1 per cent of the culture must be resistant to streptomycin in order for bacilli to grow in a medium containing streptomycin. Williston and Youmans (13) noted the effect of a solid medium in decreasing the sensitivity to streptomycin, while the use of Tween medium increased the sensitivity to streptomycin. Obviously it is not possible to identify the effects of these various factors as they occur, but they must be kept in mind in interpreting the clinical significance of isolated drug-sensitivity studies.

Youmans and Karlson (1) have reported the rapid emergence of resistant tubercle bacilli within twelve days of the beginning of streptomycin therapy. In table 4 it is shown that resistance existed before streptomycin therapy and was noted at eleven weeks but not in the intervening period in the present series. Full discussion of this finding would involve complete data on all negative cultures obtained and is not within the scope of this paper.

Another possible explanation of the pattern of resistance seen in these children may lie in the fact that, when the total number of organisms is low, the absolute number of resistant variants is fewer than in adults; therefore, resistance as reflected in a conversion from negative to positive cultures may be delayed.

Dissociation in the degree of sensitivity of organisms from different sources was noted in 3 patients. In each case, tubercle bacilli obtained from gastric washings were sensitive, while organisms obtained on bronchial aspiration were

resistant. Other observers have remarked on the same phenomenon of dissociation in resistance in organisms in cultures obtained from different sources or even from different sites in the lung field (14, 15).

The cases of 4 patients were of particular interest in that changes occurred in the drug sensitivity of cultures obtained long after streptomycin had been discontinued. If these changes in drug sensitivity really occurred at this time it bears out the suggestion that organisms which are fully sensitive at the end of treatment may become resistant when the chemotherapeutic agent is removed (16).

It is not possible to speak of the present results in terms of incidence of occurrence of resistance, in view of the differences in degrees of resistance, in the diagnoses of the patients, and in the sources of cultures. The emergence of resistance was seen only in 3 patients. In one, a slow increase in the resistance of the tubercle bacilli in the cerebrospinal fluid was observed over an extended period; and in another patient, resistance to 1,000 γ of streptomycin per ml. was demonstrated during treatment of relapse of meningitis. A third patient with miliary tuberculosis already had drug-resistant tubercle bacilli before treatment and the organisms remained predominantly resistant throughout treatment. The 2 patients with meningitis died, while the child with miliary tuberculosis did not respond to treatment with streptomycin. In the 14 other patients, it is not desirable to describe as "emergence" the presence of resistant organisms of varying degrees of resistance to streptomycin, especially when these resistant organisms occurred in an isolated culture or when subsequent cultures contained sensitive organisms; especially since all of these 14 patients did well clinically and have not had further positive cultures at the time of writing.

In general, the paucity of consistently resistant tubercle bacilli obtained from the children in this series suggests that the main difference between such a group and the adult group may be the number of organisms present in the source from which the culture is taken. This is borne out by the general impression that resistance is relatively rare in cultures from patients with meningitis in which relatively few organisms are obtained, and higher in cultures obtained directly from sources rich in organisms. It is also supported by the fact that, although an incidence of emergence of resistance comparable to the incidence noted in adults treated for chronic pulmonary tuberculosis might be expected in the children with chronic pulmonary tuberculosis and progressive primary tuberculosis, no such incidence was noted in the present series. Moreover, there was no failure of clinical response to therapy in the children whose cultures of tubercle bacilli exhibited an inconsistent resistance to streptomycin.

SUMMARY

Cultures of *M. tuberculosis* obtained from 152 children less than thirteen years of age were tested for the sensitivity of the tubercle bacilli to streptomycin. One hundred and eighty-seven of the cultures studied were obtained from 115 patients not yet treated with streptomycin, while 200 cultures were obtained from 59 patients after the beginning of streptomycin therapy. Only 17 patients had a

total of 46 cultures with tubercle bacilli resistant to 10 γ or more of streptomycin per ml. Five of these patients, with 7 cultures, had not previously been treated with streptomycin. In the present series, the diagnosis, source of culture material, duration of streptomycin therapy, and degree of resistance varied greatly. Inconstancy in the occurrence of resistance to streptomycin was present and the reasons for the inconstancy, including the effect *in vivo* and *in vitro* of a small inoculum, were discussed.

SUMARIO

La Ocurrencia de Bacilos Tuberculosos Resistentes a la Estreptomicina en los Niños Tuberculosos

Cultivos del *M. tuberculosis* obtenidos de 152 niños de menos de trece años de edad fueron comprobados con respecto a la sensibilidad de dichos bacilos a la estreptomicina. Ciento ochenta y siete de los cultivos estudiados procedían de 115 enfermos no tratados todavía con estreptomicina, en tanto que 200 procedían de 59 enfermos en que ya se había iniciado la estreptomicinoterapia. Nada más que 17 enfermos rindieron un total de 46 cultivos con bacilos tuberculosos resistentes a 10 o más γ de estreptomicina por ml. Cinco de ellos, con 7 cultivos, no habían sido tratados antes con estreptomicina. En la serie actual, variaron considerablemente el diagnóstico, procedencia del material de cultivo, duración de la estreptomicinoterapia e intensidad de la resistencia. Hubo inconstancia en la ocurrencia de resistencia a la estreptomicina, y se discuten las razones de esa inconstancia, comprendiendo el efecto *in vivo* e *in vitro* de un pequeño inóculo.

RESUME

La occurrence de bacilles tuberculeux résistants à streptomycine des enfants atteints de tuberculose

Des bacilles provenant de cultures de *M. tuberculosis* obtenues chez 152 enfants âgés de moins de treize ans ont été soumises au test de sensibilité à la streptomycine. Parmi les cultures étudiées, 187 provenaient de 115 malades non encore traités par la streptomycine, tandis que 200 cultures provenaient de 59 malades ayant commencé un traitement par la streptomycine. La présence de bacilles tuberculeux résistants à 10 γ ou plus de streptomycine par ml. n'a été rencontrée que chez 17 malades seulement, le nombre total de cultures étant de 46. Cinq de ces malades, le nombre de cultures étant de 7, n'avaient pas été préalablement soumis à la streptomycinothérapie. Dans les séries étudiées, le diagnostic, la source du matériel de culture, la durée de la streptomycinothérapie et le degré de la résistance ont été très variables. Le phénomène de résistance à la streptomycine s'est montré inconstant et les raisons de cette variabilité, y compris l'action *in vivo* et *in vitro* d'un inoculum réduit, sont étudiés.

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Case Reports

ICTERUS IN ACUTE MILIARY TUBERCULOSIS[1]

Report of a Case Simulating Leptospiral Jaundice

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INTRODUCTION

When miliary tuberculosis involves the liver, the resulting condition often challenges the diagnostic acumen of the clinician (1). Despite the fact that autopsy often reveals involvement of the liver in acute miliary tuberculosis (2, 3), the appearance of jaundice during the clinical course of the disease is not common (4–6). In the case which forms the basis for the present report, the presence of febrile jaundice and hemorrhagic manifestations, signs usually considered typical of Weil's disease, complicated the problem of diagnosis. The occurrence of epididymitis, pneumonitis, and a relative lymphocytosis, however, offered clues pointing to tuberculosis as the causative factor.

CASE REPORT

E. W., a 39-year-old, white businessman, entered the hospital on the seventh day of an acute febrile illness which had begun with malaise, sore throat, and an elevation of oral temperature to approximately 102°F. He also complained of nausea, vomiting, hiccuping, and epistaxis. He had developed a cough which was productive of blood-streaked sputum and had noticed frequent loose stools of normal color. The patient was hospitalized when it was discovered that the sclera of his eyes was of a slight yellow tint.

Past history: In 1935 the patient had an acute, tender enlargement of the right epididymis of two weeks' duration, followed by residual swelling. The acute swelling, with redness and tenderness, had recurred one week before his admission to the hospital. There was no history of excessive intake of alcohol or of known hepatotoxins.

Physical examination: Examination on entry to the hospital revealed an acutely ill patient in obvious respiratory distress. He was severely dehydrated and somewhat confused. The oral temperature was 101°F., the pulse rate 96 a minute, and the respiratory rate 30 a minute. The conjunctivas were conspicuously injected, and the scleras moderately icteric. The nose contained a small amount of dried blood. The pharynx was intensely injected and there was an inspissated exudate on the posterior wall. There was no rigidity of the neck. On percussion, the heart was not enlarged and no murmurs or arrhythmias were detected. The blood pressure was 130 systolic, 70 diastolic in mm. of mercury. On examination of the chest, scattered areas of subcrepitant rales and bronchial breathing were heard. A blunt hepatic margin, not tender, was felt 7 cm. below the right costal margin. The spleen was not palpable. The scrotal skin was red and indurated; the right testis was enlarged, measuring approximately 3 by 4 by 4 cm.; most of the swelling was in the posterior-superior pole. Rectal examination showed no abnormalities. The deep tendon reflexes were bilaterally hyperactive, and ankle clonus was present. Roentgenograms of the chest were interpreted as showing a central pneumonia of the upper lobe of the right lung and severe bronchitis at the base of both lungs.

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Laboratory examination showed the following results: The hemoglobin was 14.5 gm. per 100 ml. The leukocytes numbered 5,000 per cu. mm. The differential count showed 41 per cent lymphocytes; some were large atypical forms and had fenestrated nuclei. The urine was amber and cloudy and contained 2-plus albumin and a few leukocytes. The icterus index was 28 units; cephalin flocculation, 1 plus; serum albumin, 2.1 mg. per 100 ml.; serum globulin, 2.3 gm. per 100 ml.; the albumin-globulin ratio was 0.9. Pharyngeal smears showed a small number of gram-negative rods and a few gram-positive cocci. The prothrombin concentration was 40 per cent. Agglutinations were negative in all dilutions for heterophile antibodies, typhoid, paratyphoid A and B fevers, undulant fever, and tularemia. A coccidioidin skin test was negative. Culture of the blood revealed no growth during a fourteen-day period.

Course: The clinical course was unfavorable and was marked by complete disorientation, generalized mild clonus, and positive extensor plantar responses. The patient developed frank hematemesis, increasing epistaxis, and the icterus increased. Examination of the cerebrospinal fluid at this time showed it to be normal. The sputum became thick and brownish and, when cultured, yielded a heavy growth of *Monilia*. No discrete areas of pulmonary consolidation developed, but scattered, fine rales persisted. Periumbilical ecchymosis appeared and became progressively more severe. The abdomen became distended. Darkfield examination of centrifuged urine sediment showed several motile, spirochetal organisms. Three subsequent agglutination tests for leptospirosis icterohemorrhagica and leptospirosis canicola, however, were negative. The complement fixation reaction with Q-fever antigen was negative. The leukocyte count rose from 5,000 per cu. mm. at the time of admission to 22,000 per cu. mm. shortly before death, and a persistent lymphocytosis was noted throughout hospitalization. The patient received a total of 5.0 gm. of dihydrostreptomycin (given in doses of 0.25 gm. every four hours) during the last four days of his illness.

The patient became progressively worse and developed evidence of renal insufficiency. The nonprotein nitrogen of the blood was 80 mg. per 100 ml., and the urea nitrogen was 30 mg. per 100 ml. Loss of blood, which was evidenced by bright red blood from the rectum and dark, tarry stools, was replaced by transfusions. Despite treatment, including the administration of aureomycin, penicillin, streptomycin, and lipotropic substances, the patient became stuporous on the fifteenth day of his illness and died.

Autopsy Report

Gross examination: An autopsy was performed two hours after death. Pronounced icterus of the skin and scleras were observed. A large area of ecchymosis was seen on the skin about the umbilicus. No adenopathy was demonstrable. Induration and enlargement of the right epididymis were noted. Considerable hemorrhage in the fat and skeletal muscle of the anterior abdominal wall was observed. Approximately two liters of dark yellow fluid were present in the peritoneal cavity. Many fibrous intraperitoneal adhesions were found on the superior surface of the liver, about the gallbladder, in the right lower quadrant, and in the pelvis. The anterior edge of the liver extended 2.0 to 3.0 cm. below the right costal margin and the xiphoid process.

Each pleural cavity contained 400 cc. of clear, dark yellow fluid; there were no adhesions. The mediastinal lymph nodes were not unusual.

There was slight enlargement of the heart (450 gm.). Several small epicardial hemorrhages were noted. A moderate degree of coronary atherosclerosis without significant vascular narrowing was observed. Considerable amounts of sanguinous mucus were present in the trachea and major bronchi. The left lung weighed 710 gm., and the right, 740 gm. Both were moderately firm and showed considerable diffuse congestion. Large amounts of sanguinous frothy fluid exuded from the cut surfaces. No tuberculous lesions were observed on macroscopic examination of the lungs.

The liver was enlarged and weighed 2,940 gm. (figure 1). The anterior margin was rounded. The capsular surface was smooth and light tan in color. The hepatic paren-

chyma generally appeared pale. The central portion of each lobule was yellow, while the peripheral portion was pale tan. The lobules appeared to be surrounded by a narrow zone of glistening translucent tissue. No distinct tubercles were observed.

The gallbladder and extrahepatic bile ducts were normal. The spleen was enlarged and weighed 430 gm. The splenic parenchyma was soft, congested, and hyperplastic. No lymphoid follicles or tubercles were seen. There were no abnormalities of the pancreas. Scattered small hemorrhages were present in each adrenal gland.

Each kidney weighed 220 gm. (figure 2). There was no capsular adherence; the cut surfaces bulged slightly, and the cortical layers appeared pale and opaque. Icteric staining was minimal. The renal pelves, ureters, bladder, and prostate gland appeared entirely normal. The testicular parenchyma was pale and soft.

The right epididymis was diffusely enlarged and averaged 1.5 cm. in diameter (figure 3). It was firm and entirely fibrotic. Several caseous tubercles were visible on section, the

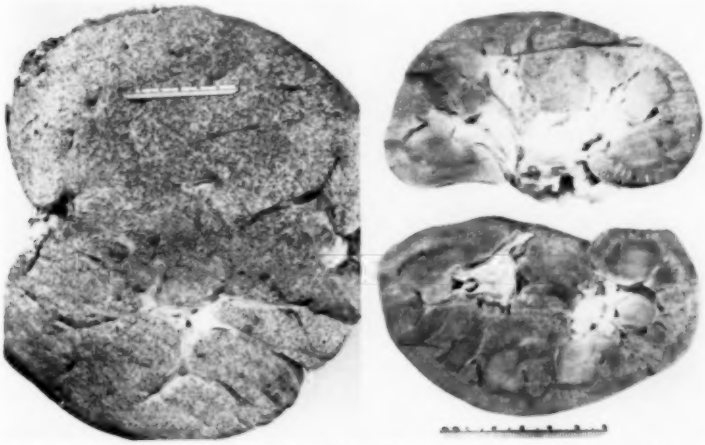

FIG. 1. (Left) Liver showing bile staining and accentuation of lobular markings.
FIG. 2. (Right) Kidney.

largest of which measured 0.5 cm. in diameter. Several small abscesses containing green purulent fluid also were present.

Multiple petechial hemorrhages were scattered throughout the gastroenteric tract. Dark blood filled the entire tract.

The aorta showed minimal sclerosis. The vena cava and iliac vessels showed no abnormalities. The marrow from several skeletal sites was hyperplastic and of a deep red color.

The brain was of normal size and weighed 1,520 gm. There were no intracranial vascular abnormalities. No arachnoidal exudate was observed. Sectioning revealed considerable congestion of the basal cerebral nuclei. The pituitary gland was normal.

Microscopic examination: The pericardial layer was normal. There were several collections of lymphocytes in the interstitial tissues but no tubercles were present. In several of the larger myocardial arteries edema of the layers was noted; it was most pronounced in the adventitia. The myocardial fibers in the endocardial layer were normal. One of the major coronary arteries had a large, fibrous intimal plaque which half occluded the lumen.

There was moderate vascular congestion of the lungs. Many alveoli were emphysematous

and contained numerous macrophages filled with carbon pigment. Several zones of scarring associated with lymphocytic infiltration were seen in the interstitial tissues. Poorly defined tubercles, composed of loosely arranged epithelioid cells, were scattered throughout the pulmonary tissue. In general, they occurred in the alveolar walls, although some projected into alveolar spaces. No necrosis, peripheral scarring, or lymphocytic infiltration of the pulmonary tubercles was evident.

There was pronounced alteration of the hepatic lobules. The central veins were dilated. The central hepatic cells in general were separated by an edematous supporting stroma; they contained large amounts of golden-brown pigment. In the peripheral portions of the lobules the majority of hepatic cells contained large and small lipid vacuoles. Throughout the hepatic tissue were numerous tubercles which tended to coalesce and which had replaced large segments of hepatic lobules (figure 4). The tubercles generally lay at the periphery of the lobules and, in some instances, almost completely surrounded individual lobules by their coalescence. Some tubercles, however, were found in central or mid zonal portions of the lobule. These hepatic tubercles were poorly defined, consisted largely of epithelioid cells, and were infiltrated with, and surrounded by, lymphocytes (figure 5).

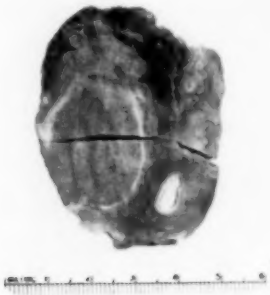

FIG. 3. Right testis and epididymis. Note enlargment of epididymis with large tubercles.

The central portions of some lobules showed minimal cellular degeneration and necrosis. True caseation was not present; minimal peripheral fibrosis was evident in a few tubercles. Even in the absence of definite tubercles, the portal areas were generally infiltrated with lymphocytes and neutrophilic leukocytes. Small bile ducts and biliary canaliculi did not contain bile. The hepatic capsule was thickened, edematous, and fibrotic. The mesothelial cells were prominent on the surface. The edematous capsule was moderately infiltrated with large macrophages, many of which had moderately abundant non-granular eosinophilic cytoplasm, and with lymphocytes.

The layers of the gallbladder were normal.

The splenic follicles were normal in size and number. The pulp showed considerable congestion. It contained scattered, small, poorly defined tubercles composed entirely of epithelioid cells with a few surrounding lymphocytes. No necrosis was evident.

Small collections of lymphocytes were present in the pancreatic interstitial tissue.

Although there was no increased cellularity of the glomeruli, the basement membranes appeared indistinct and frayed. The glomerular spaces generally contained precipitated protein material. Considerable cloudy swelling and degeneration of the convoluted tubular epithelial cells were noted. Interstitial edema was present. Small collections of lymphocytes were observed near the corticomedullary junction. Many tubules contained bile-stained hyaline casts. Collections of lymphocytes were found in the pelvic connective tissues.

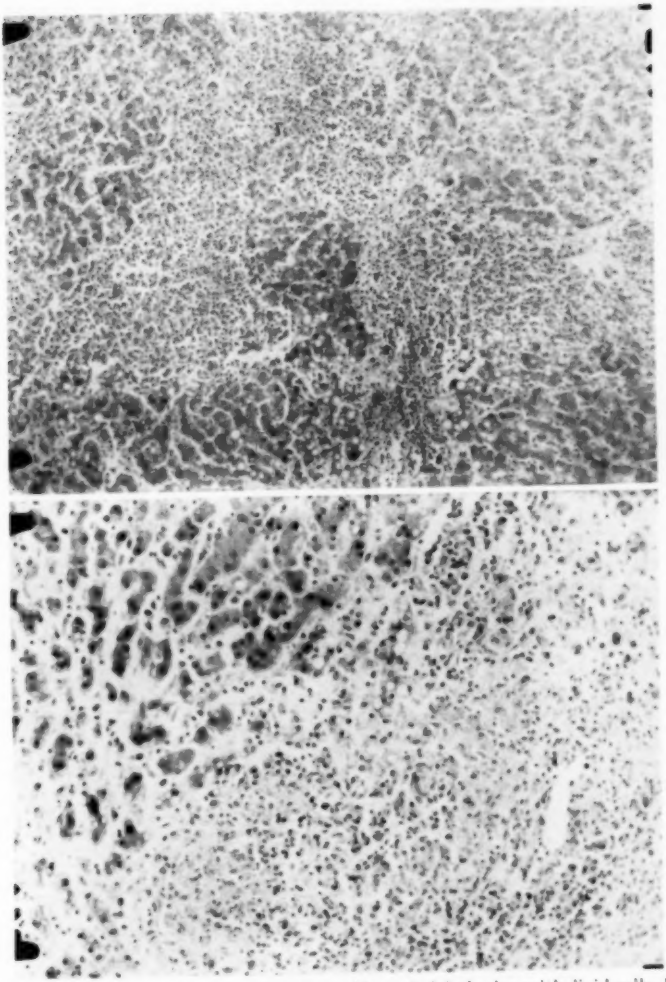

FIG. 4. Liver showing partial replacement of hepatic lobules by epithelioid cells. Hematoxylin and eosin.

Top—(×80)
Bottom—(×160)

The layers of the bladder were normal except for scattered lymphocytes in the subepithelial layer. There was mild lymphocytic infiltration of the prostatic stroma, but no tubercles were present.

The tubules of the right testis generally showed minimal spermatogenesis. Many groups of tubules were atrophic and were replaced by hyaline fibrous tissue. Extensive interstitial

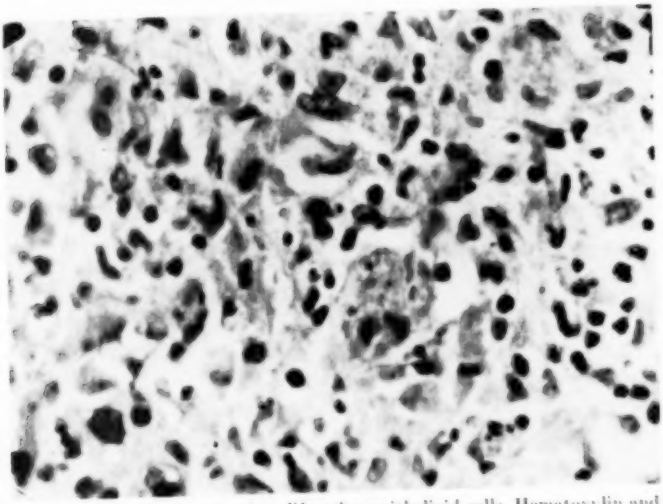

FIG. 5. Liver showing periportal proliferating epithelioid cells. Hematoxylin and eosin. (×320)

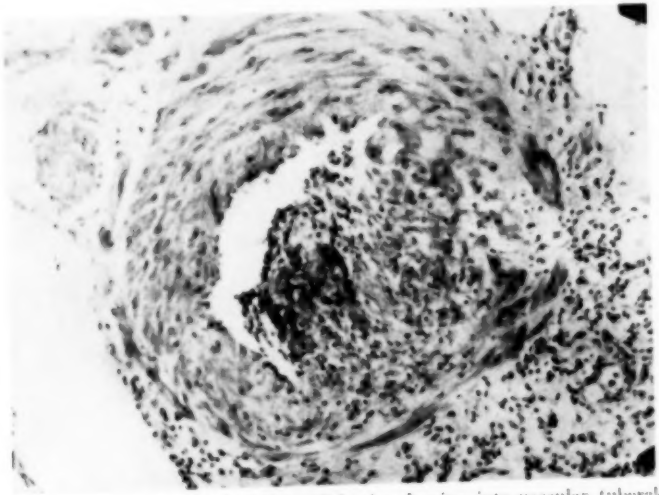

FIG. 6. Artery in capsule of right epididymis, showing intravascular tubercle with thrombosis. Hematoxylin and eosin. (×160)

edema and fibrosis were noted. This interstitial tissue was heavily infiltrated with lymphocytes, plasma cells, and rather numerous large mononuclear cells with non-granular eosinophilic cytoplasm. Tubercles were not observed in the testicular parenchyma. The tunica

vaginalis was extremely thickened and heavily infiltrated with chronic inflammatory cells. Near the periphery were a few small tubercles composed of epithelioid cells without caseation.

No tubules remained in the right epididymis. The normal tissue was replaced by large caseous tubercles which were rimmed with proliferating epithelioid cells and a few Langhans' giant cells. At the periphery of this layer were infiltrating lymphocytes and a moderate degree of fibrosis. The areolar tissue and fat surrounding the epididymis contained numerous small tubercles, infiltrated sparsely with giant cells and diffusely with chronic inflammatory cells. None showed fibrosis or caseation. The intimal layers of some of the small arteries and veins of the right epididymis contained tubercles which were often associated with organizing thrombi (figure 6). Other vascular changes included proliferative intimal lesions without an inflammatory reaction.

The thyroid and pituitary glands appeared normal.

The aortic intima was thickened and consisted of loosely arranged connective tissue. The adventitial and medial layers were not abnormal.

The serosal layer of the stomach showed swelling and prominence of the mesothelial cells. The underlying connective tissue was edematous, showed early fibroblastic proliferation and infiltration with lymphocytes and large macrophages with abundant eosinophilic cytoplasm. Similar changes were observed in the mucosa and serosa of the large and small bowels.

In the hilar lymph nodes were a few peripherally placed small tubercles, composed of epithelioid cells with a few multinucleated giant cells. In the peripheral sinusoids there were numerous macrophages, many of which were large and had abundant agranular eosinophilic cytoplasm. Some were multinucleated.

The bone marrow of the lumbar spine was hyperplastic and contained diminished numbers of fat cells. The foci of nucleated erythrocytes were larger and more numerous than normal, but showed normal maturation. The myeloid cells were increased and showed a predominance of neutrophilic myelocytes. Megakaryocytes were present in normal numbers. There were a few small, poorly defined, noncaseating tubercles composed of epithelioid cells and lymphocytes.

Numerous acid-fast organisms morphologically resembling tubercle bacilli were observed in the caseous tubercles of the right epididymis. None were found in the small, noncaseating miliary tubercles of the lungs, liver, or other tissues.

COMMENT

Hepatic tuberculosis may manifest itself by solitary or conglomerate tubercles, by tuberculous cirrhosis, or by periportal miliary tubercles. The latter, which result from hematogenous spread via the portal vein or hepatic artery, have been reported as the most common form of hepatic tuberculosis (7). Chapman and Whorton (2), in a series of autopsies in 61 cases of acute generalized miliary tuberculosis, reported hepatic involvement by miliary tubercles in all, although none of the patients had shown clinical evidence of jaundice. Warthin (8), however, stated that 80 per cent of his patients with acute generalized miliary tuberculosis of the typhoid form showed some degree of jaundice. When jaundice does occur, it is the result of either intra-acinar biliary capillary obstruction (9) or periportal pressure (10). According to Warthin (8), no relationship between the degree of hepatic involvement and icterus can be established. Cruice (11), however, concluded that intense jaundice is due to pressure of lymph nodes or solitary tubercles on extrahepatic ducts and that the milder forms of jaundice are due to the presence of miliary tubercles.

In the present case, the miliary disease originated from chronic tuberculosis of the right epididymis. In this lesion there was microscopic evidence of intravascular extension of the tuberculous process. It seems likely that dissemination of tubercle bacilli occurred through the testicular venous system to the vena cava and pulmonary circulation, and

thence to the arterial system. That the hepatic disease resulted from hepatic arterial dissemination was indicated by the presence of miliary tubercles in the spleen and bone marrow as well. Dissemination via the portal system seems highly improbable, in spite of the overwhelming involvement of the liver.

Although tubercle bacilli were not demonstrable in any of the lesions, other than those in the epididymis, and although many of the miliary tubercles had an atypical appearance, the tuberculous nature of the miliary process seemed definite.

Although miliary tuberculosis was widespread, it was most severe in the liver and was characterized by a diffuse perilobular arrangement of noncaseating, coalescing tubercles. It seemed apparent that jaundice had resulted from obstruction of biliary canaliculi at the periphery of the hepatic lobules.

The absence of tubercle bacilli in the miliary lesions, including those in the liver, and the presence of early minimal fibroblastic proliferation with deposition of collagenous fibers in some tubercles suggested that the lesions had been modified by the administration of streptomycin. The subsequent healing had not progressed to the extent described in reports on the use of streptomycin in other patients (12–15), undoubtedly because of the small amount administered and the short period of treatment. It should be recalled, however, that the early report of Warthin (16) also described noncaseating, perilobular epithelioid cellular proliferation, but in his patients many tubercle bacilli were observed in the hepatic lesions. The absence of tubercle bacilli in miliary lesions may be one result of treatment of tuberculosis with streptomycin. There was no apparent modification of either the large caseous lesion or the smaller satellite tubercles in the right epididymis by the streptomycin.

SUMMARY

A case of acute miliary tuberculosis with icterus simulating Weil's disease is presented. The clinical combination in a patient of hepatomegaly, fever, icterus, hemorrhage, and delirium, symptoms characteristic of the so-called typhoidal state, should suggest the possibility of acute miliary tuberculosis of the liver.

SUMARIO

La Ictericia en la Granulia Aguda. Presentación de un Caso que Simulaba Ictericia Leptospiral

En el caso presentado, una tuberculosis miliar aguda estaba acompañada de ictericia, simulando enfermedad de Weil. La combinación clínica en un enfermo de hepatomegalia, fiebre, ictericia, hemorragia, y delirio, síntomas de típica del llamado estado tifoideo, debe indicar la posible existencia de granulia aguda del hígado.

RESUME

Ictère dans la miliaire aiguë et observation d'un cas simulant la leptospirose ictéro-hémorragique

Publication d'un cas de miliaire aiguë, s'accompagnant d'ictère et simulant la Maladie de Weil. Lorsque, chez un malade, les signes cliniques suivants se manifestent: hépatomégalie, fièvre, ictère, hémorragie et délire, symptômes caractéristiques de l'état dit "typhoïde", il y a lieu d'envisager le diagnostic de tuberculose miliaire aiguë du foie.

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PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS COMPLICATED BY PREGNANCY[1]

MAX PREMINGER

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INTRODUCTION

General agreement seems to exist that pneumoperitoneum should be instituted immediately post partum in suitable cases of pulmonary tuberculosis. There is hardly any evidence in the literature, however, to support the use of pneumoperitoneum during pregnancy; rather, it is generally believed that pregnancy constitutes a definite contraindication (1). Nevertheless, Banyai (2) does not offer any objections to the application of pneumoperitoneum in pregnancy; and Stein (3), as mentioned by Banyai, thinks it practicable with small amounts of oxygen. Vajda (4) advocates pneumoperitoneum toward the end of term in order to prevent the descent of the diaphragm after delivery. The use of pneumoperitoneum "intrapartum" (5) has also been described; Banyai, and Sahn and Bass (6) have reported cases in which pneumoperitoneum was continued in a patient who became pregnant during treatment.

The occasions in which pneumoperitoneum could be considered preferable to other methods of therapy must arise with relative infrequency. In the case to be reported, no detrimental effects were observed after pneumoperitoneum had been instituted without prior knowledge that a pregnancy of two or two and one-half months' gestation existed. The patient had denied any amenorrhea or other menstrual irregularities.

CASE REPORT

A. N., an 18-year-old white woman, was admitted on December 30, 1949. When she had entered high school in October, 1945, at the age of fourteen, her cutaneous reaction to tuberculin was positive (patch test). A chest roentgenogram during November, 1945, was presumed to have been normal, since she did not hear anything to the contrary. In December, 1945, she developed a productive cough, and this time a lesion diagnosed as tuberculous was evident on the roentgenogram. The patient was then treated with bed rest at home but received pneumoperitoneum at the physician's office. Apparently she improved under this regimen, as she was permitted to return to school in September, 1946. Two months later, however, she again started to cough productively and to lose weight, so that she had to quit school. She remained at home and was treated with bed rest only. By the summer of 1949, she appeared to be sufficiently stabilized to permit some activity, but a serial chest film in November, 1949, a month before admission, revealed fresh lesions which were considered to be tuberculous in nature.

The patient's general condition was good on admission to the hospital. A slight cough, productive of approximately 4 cc. of thick greenish sputum in twenty-four hours, was the only complaint. The sputum was positive for acid-fast bacilli (Gaffky V). The patient had suffered from bronchial asthma until the age of eight. Her mother had died of pulmonary tuberculosis in 1940 at the age of twenty-eight years. Her maternal grandmother had also been afflicted with pulmonary tuberculosis.

The temperature, pulse, and blood pressure were normal. The posterior cervical lymph nodes were somewhat enlarged, discrete, and nontender bilaterally. Diminished resonance and medium moist rales were found over both upper halves of the lung fields anteriorly and posteriorly.

[1] From the Marcus W. Newcomb Hospital for Chest Diseases, New Lisbon, New Jersey.

FIG. 1

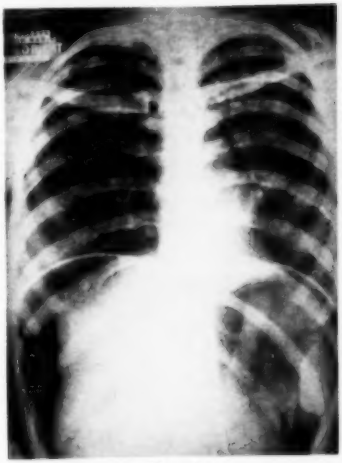

FIG. 2

FIG. 1. (January 3, 1950): Admission roentgenogram shows two cavities in the left mid-lung field, the larger one containing a sputum level.

FIG. 2. (March 18, 1950): The cavities are no longer evident one month after the institution of pneumoperitoneum.

FIG. 3

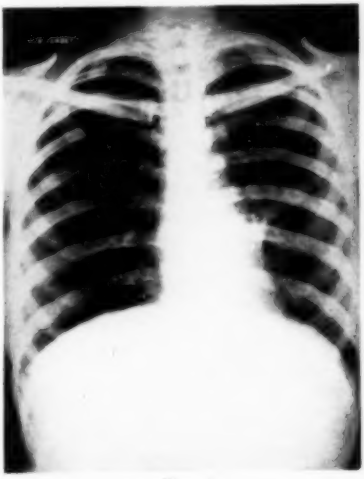

FIG. 4

FIG. 3. (June 15, 1950): Cavities have remained closed. Pneumoperitoneum had to be discontinued five days later.

FIG. 4. (November 6, 1950): Readmission roentgenogram appears unchanged except for the absence of pneumoperitoneum.

The chest roentgenogram on admission to the hospital revealed soft mottling throughout both upper halves. In the left mid-lung field two cavities, 2 by 2 cm. and 5 by 3 cm. in diameter, respectively, were evident, the larger one containing a fluid level. The results of the blood count were: hemoglobin, 13.0 gm. per 100 ml.; erythrocytes, 4,380,000 per cu. mm.; leukocytes, 7,650 per cu. mm., with 70 per cent neutrophils, 20 per cent lymphocytes, 8 per cent monocytes, and 2 per cent eosinophils. The erythrocyte sedimentation rate was 28 mm. in one hour (Cutler). A serologic test for syphilis (Mazzini) was negative. The urine was normal. The patient was placed on strict bed rest and received 0.5 to 1.0 gm. of dihydrostreptomycin daily for a total of 32 gm.

Artificial pneumoperitoneum was instituted on February 14, 1950, and 1,000 cc. of air were given. The procedure was repeated the next day and on February 17, 1950. Further refills of 800 to 1,200 cc. of air followed at twice weekly and later at weekly intervals, ef-

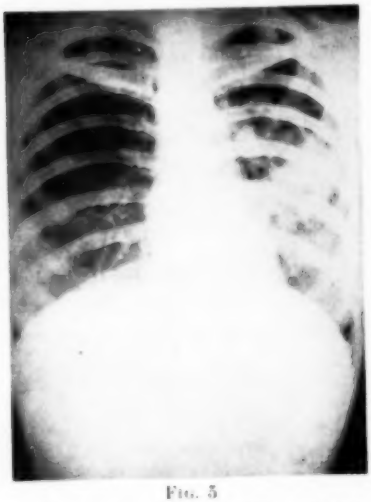

FIG. 5

FIG. 6

FIG. 5. (December 21, 1950): The large cavity in the left mid-lung field has opened up.

FIG. 6. (January 7, 1952): The cavity in the left mid-lung field has been closed for the past six months.

fecting a rather moderate rise of the diaphragm. The sputum was found negative for acid-fast bacilli for the first time in April, 1950. Of four consecutive 144 hour concentrated specimens, the last two in May, 1950, were positive for acid fast bacilli (Gaffky II). On June 20, 1950, approximately the twenty-fifth week of gestation, it became necessary to discontinue the pneumoperitoneum refills because of technical difficulties due to the ascent of the uterus, the fundus being palpable four fingers above the umbilicus. The cavities in the left mid-lung field were no longer discernible.

On September 11, 1950, the patient entered the Burlington County Hospital, Mt. Holly, New Jersey, as she appeared ready for delivery. Radiologic pelvimetry (Snow method) revealed a small android pelvis with prominent ischial spines. The fetal head in right occipito-posterior position appeared large in proportion to the pelvis. In view of these findings and the fact that it was her first child, prolonged labor had to be anticipated and it was believed such a course should be avoided. Therefore, a low cervical cesarean section was decided on and performed on September 12, 1950. A viable normal male infant who weighed 8 pounds, 13 and one-half ounces was extracted. The postoperative course proved

uneventful. Pneumoperitoneum was not instituted post partum as the patient preferred to return home for a while.

The patient was readmitted on November 6, 1950. A chest film did not reveal any changes suggesting activity of the tuberculosis. Sputum could not be obtained. During the second half of December, 1950, she began to cough productively again, and the chest roentgenogram showed that the large cavity had reopened. She was given dihydrostreptomycin intramuscularly, 1 gm. daily, for a total of 20 gm. and by aerosol, 0.5 gm. divided in 8 doses, every day for six weeks. She was also started on para-aminosalicylic acid, 12 gm. daily, which was continued for six months. Pneumoperitoneum was instituted again.

The ensuing course was free of complications. At present, fifteen months after her second admission, the patient is entirely asymptomatic and there is no evidence of cavitation on routine films and planigrams. Concentrated sputum specimens (72 and 144 hours) have been repeatedly negative for acid-fast bacilli, and a recent gastric culture has been negative for *M. tuberculosis*. The erythrocyte sedimentation rate is 10 mm. in one hour (Cutler). Pneumoperitoneum is being maintained by refills of 1,000 to 1,200 cc. of air at intervals of ten to fourteen days.

SUMMARY

A case of far advanced pulmonary tuberculosis complicated by pregnancy is described in which pneumoperitoneum was instituted during the third month of gestation and continued until prevented by the ascent of the uterus. A viable normal infant was delivered by cesarean section. The necessity of instituting pneumoperitoneum immediately post partum has been demonstrated.

SUMARIO

El Neumoperitoneo en el Tratamiento de la Tuberculosis Pulmonar Complicada con Embarazo

En el caso descrito de tuberculosis pulmonar muy avanzada y complicada por el embarazo, se instituyó el neumoperitoneo durante el tercer mes de la gestación, continuándose hasta que lo impidió el ascenso del útero. Con la cesárea se extrajo un feto normal viable. Queda también demostrada la necesidad de instituir el neumoperitoneo inmediatamente después del parto.

RESUME

Le pneumopéritoine dans le traitement de la tuberculose pulmonaire compliquée par la gestation

Description d'un cas de tuberculose pulmonaire très avancé et compliqué par la grossesse, dans lequel le pneumopéritoine avait été instauré au troisième mois de la gestation et maintenu jusqu'au moment où il a été prévenu par l'ascension de l'utérus. Un enfant normal vivant a été extrait par section césarienne. La nécessité d'instaurer un pneumopéritoine immédiatement après l'accouchement a été démontrée.

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RIGHT-SIDED SPONTANEOUS PNEUMOTHORAX AND PERITONEAL EFFUSION COMPLICATING THERAPEUTIC PNEUMOPERITONEUM[1]

FRANCO NOZZOLI, LAZAR EPSTEIN, AND LADISLAO MOLNAR[2]

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INTRODUCTION

The growing popularity of pneumoperitoneum in the treatment of pulmonary tuberculosis is accompanied by an increase in the number of reports on its complications. In concluding his review on this subject, Stein (5) states that "of all patients who receive artificial pneumoperitoneum, approximately 5 to 6 per cent will develop complications serious enough to make continuation of therapy impossible." One of the potentially serious complications is spontaneous pneumothorax. More than twenty cases of this complication were reported in recent years by Yannitelli, Woodruff, Mueller, and Howard (1), Ross and Farber (2), Repa and Jacobson (3), Wu and Neptune (4), and other writers.

The present report is concerned with a nonfatal case of spontaneous pneumothorax and peritoneal effusion in the course of pneumoperitoneum.

CASE REPORT

S. L., a 22-year-old male, was admitted to the sanatorium on November 2, 1946. Two years prior to admission, in November, 1944, while he was hospitalized at another institution for exudative pleurisy on the left side, a roentgenogram of the chest revealed "bilateral pulmonary infiltration." In May, 1946, extrapleural pneumonolysis on the left was performed after a long period of bed rest and unsuccessful attempts to induce pneumothorax had failed to control a cavitation in the left lung.

Physical examination on admission revealed a young male in good general condition, weighing 75 kg. He had moderate cough productive of small amounts of sputum positive for acid-fast bacilli on direct smear. The erythrocyte sedimentation rate was 5 mm. in the first hour (Westergren). A roentgenogram of the chest of November 7, 1946 (figure 1) showed an extrapleural pneumothorax occupying the upper part of the left hemithorax and an area of increased transparency, 3 by 2 cm. in size, between the sixth and seventh ribs posteriorly. The extrapleural air-pocket and the radiolucent area, the latter consistent with tuberculous cavitation, were clearly visible on the 8 cm. level of a tomogram taken shortly after admission (figure 2).

Since cavity closure could not be obtained, in spite of the high pressures maintained in the extrapleural space, a *pneumoperitoneum* was induced on January 14, 1947, supplemented by left phrenic crush on April 10, 1947. Roentgenographic examination on September 1, 1947 (figure 3) revealed the presence of air beneath the dome of the diaphragm, with elevation of it on both sides, in addition to the extrapleural pneumothorax on the left side, with no evidence of the cavitation noted on the previous films.

On February 21, 1948, thirteen months after the induction of the pneumoperitoneum and eight days after the last refill into the peritoneal cavity, the patient noted a sudden sharp pain in his right hemithorax, accompanied by intense dyspnea; he was cyanotic and his pulse rate was 120 per minute. There was a tympanitic percussion sound over the right hemithorax in the absence of breath sounds. The screening of the chest revealed a collapse of the right lung, determined by the presence of air in the pleural cavity and the diminution of air below the diaphragm. The manometric readings in the peritoneal cavity before the last refill were plus 20, plus 22, and, after the introduction of 1,500 cc. of air, plus 24, plus

[1] From the Sanatorium of the American Joint Distribution Committee, Merano, Italy.

[2] Present address: Via La Marmora 14, Firenze, Italy.

26. The manometric readings in the pleural cavity shortly after the accident were minus 2, plus 16, and, after the aspiration of 2,000 cc. of air, minus 8, plus 2.

Twenty days later, on March 10, 1948, after the complete re-expansion of the right lung a refill was given cautiously into the peritoneal cavity. No initial manometric readings

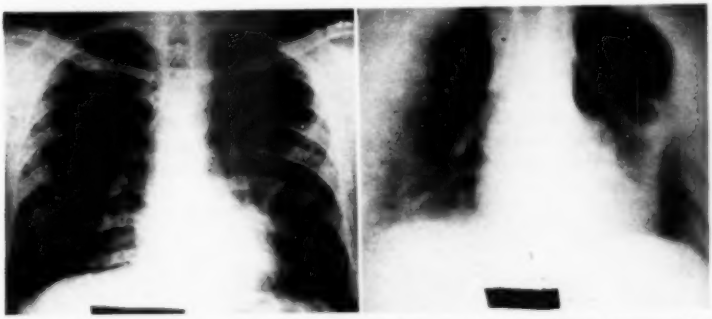

FIG. 1. (Left) Roentgenogram of chest shows the presence of extrapleural pneumothorax on the left and a ring-shadow in the collapsed lung.

FIG. 2. (Right) Tomogram of chest (8 cm. level) confirms the presence of cavitation in the collapsed left lung.

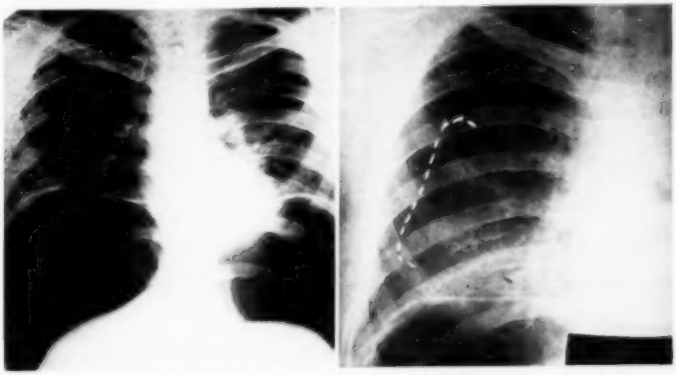

FIG. 3. (Left) Roentgenogram of chest, nine months after induction of pneumoperitoneum, shows the presence of air below the diaphragm. There is no evidence of the cavitation previously noted.

FIG. 4. (Right) Roentgenogram of chest, taken after a refill into the peritoneal cavity, shows the presence of air in the right pleural cavity and beneath the dome of the diaphragm.

were obtained. With the introduction of air with the patient in the semi-upright position, the manometer of a pneumothorax apparatus connected with a needle introduced into the pleural cavity showed a slow rise in the endopleural pressure. The passage of air from the peritoneal cavity into the right pleura was confirmed by a roentgenogram taken immediately after the refill (figure 4).

The pneumoperitoneum was resumed, and no incidents occurred until July 26, 1948, when, thirteen days after the last refill, the patient noted again a sudden sharp pain in the right shoulder, accompanied by dyspnea. The manometric readings at the last refill were plus 14, plus 16 initially, and, after the introduction of 1,000 cc. of air, plus 18, plus 22. A roentgenogram (figure 5) showed again a right-sided pneumothorax and the disappearance of the air from the abdominal cavity. After the removal of the air from the pleural cavity, the right lung re-expanded completely, and the refills into the peritoneal cavity were continued under moderately positive pressures until October, 1948, when high fever and abdominal pain appeared, followed by peritoneal effusion; a total of 6,000 cc. of serous fluid was removed on two occasions. The sediment contained only a few endothelial cells, and cultures for tubercle bacilli and other organisms remained sterile. After the second removal of the fluid, the temperature returned to normal and the effusion did not reappear. The pneumoperitoneum refills were definitively abandoned in December, 1948.

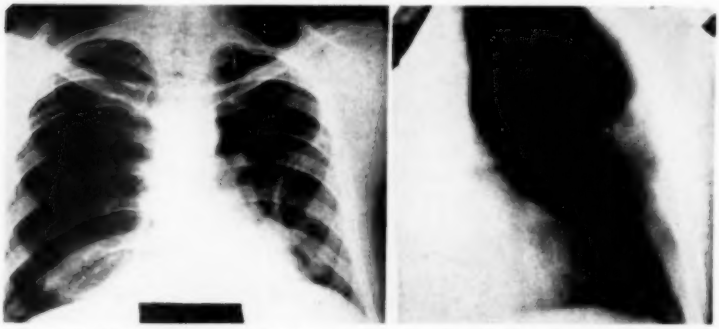

FIG. 5. (Left) Roentgenogram of chest, taken after the third occurrence of spontaneous pneumothorax on the right, shows the absence of air in the peritoneal cavity.

FIG. 6. (Right) Tomogram of chest (8 cm. level), nine months after the cessation of pneumoperitoneum, reveals fibrous changes at the site of the previous cavity on the left side.

The sputum was negative for tubercle bacilli two months after the institution of the pneumoperitoneum, and remained negative throughout the period of observation, that is, until December, 1951. The sputum examinations included numerous cultures on Petragnani medium.

Tomographic examination of the chest on July 29, 1949, nine months after the cessation of the pneumoperitoneum therapy, showed (on the 8 cm. level) the presence of the extrapleural pneumothorax and fibrotic changes at the site of the cavity previously seen (figure 6).

The patient was discharged from the sanatorium on August 29, 1949, and the extrapleural pneumothorax was continued on an ambulatory basis until September, 1950. After the complete re-expansion of the left lung he was able to resume full-time work, and his condition remained completely satisfactory. The last roentgenographic examination on September 25, 1951, showed only the presence of fibrotic changes at the site of the previous cavity. It is noteworthy that throughout the course of his illness this patient never received antimicrobial therapy.

COMMENT

It is noteworthy that the spontaneous pneumothorax occurred in the present case on the right side and on two occasions several days after a refill into the peritoneal cavity,

just as happened in other cases described in the literature. Obviously, the passage of air from the peritoneum into the pleural cavity must be due to the existence of a communication between the two cavities. A communication may be established as a consequence of the atrophy of the diaphragm resulting from phrenic crush or exeresis. It may result from inflammatory changes in the diaphragm or from a congenital defect determined by incomplete fusion of the single bundles constituting the muscle. Congenital malformations are responsible for some other complications of pneumoperitoneum (pneumomediastinum and scrotal pneumocele), characterized by the passage of air from the abdominal cavity into confining cavities with which it is connected in embryonic life.

In the event that the communications are wide between the abdominal and pleural cavities, the passage of air will take place independent of the pressure prevailing in the pneumoperitoneum. The communications, however, may be merely "*loci minoris resistentiae*" in the sense of a hernial orifice, and in this latter case only high intraperitoneal pressures will determine the passage of air into the pleural cavity. The reasons for the belief that in the present case this latter mechanism was responsible are as follows:

The first incident occurred thirteen months after the induction of the pneumoperitoneum, after the pressures in the peritoneal cavity had been brought to a high level.

On controlling the manometric readings in the pleural cavity while introducing air into the peritoneum, it was noted that only part of the air found its way into the pleural cavity. Moreover, in spite of the high pressures reached in the pneumoperitoneum, the pressure in the pleural cavity rose only slightly above the atmospheric level.

In the long interval, four months between the second and third episodes, during which the pneumoperitoneum was conducted with gradually increasing pressures, the passage of air took place only when high pressures were obtained.

It is believed that the other complication in the present case, namely, the peritoneal effusion, was also due to the high intraperitoneal pressures. The decision to continue the pneumoperitoneum in spite of these complications was based, on the one hand, on their relatively benign character and, on the other, on the very good effect of pneumoperitoneum as an adjunct collapse measure in bringing about cavity closure when extrapleural pneumothorax alone had failed.

SUMMARY

A case of pneumoperitoneum complicated by repeated right-sided spontaneous pneumothorax and peritoneal effusion is reported. These complications did not interfere with the successful continuation of the therapy.

SUMARIO

Neumotórax Espontáneo del Lado Derecho y Derrame Peritoneal como Complicación del Neumoperitoneo Terapéutico

En el caso comunicado, un neumoperitoneo terapéutico fué complicado repetidamente por la aparición de neumotórax espontáneo en el lado derecho y derrame peritoneal. Esas complicaciones no impidieron la continuación feliz de la terapéutica.

RESUME

Pneumothorax droit spontané et épanchement péritonéal compliquant le pneumopéritoine thérapeutique

Un cas de pneumopéritoine compliqué par un épanchement pleural à droite et un épanchement péritonéal est rapporté. Ces complications n'ont pas empêché de continuer cette thérapeutique avec succès.

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(2) ROSS, J., AND FARBER, J. E.: Right-sided spontaneous pneumothorax complicating therapeutic pneumoperitoneum, Am. Rev. Tuberc., 1951, *63*, 67.

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(5) STEIN, H. F.: Complications of artificial pneumoperitoneum: A review, Am. Rev. Tuberc., 1951, *64*, 645.

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Notes

A RAPID CHEMICAL TEST OF TOTAL VIABILITY FOR SUSPENSIONS OF TUBERCLE BACILLI[1]

Ten years ago it was learned[2] that tetrazolium salt, a colorless dye, is reduced by living cells to an easily detectable red compound (red formazan). Later confirmation of this process was obtained for seed embryos, bull sperm, yeasts[3], and fungi[4] by use of 2,3,5 triphenyltetrazolium chloride. These several studies offer reasonable suggestion that under constant conditions the percentage of reduction of this salt is in direct proportion to the viability of the cells. Still more recent work has further confirmed these results and attested increasing interest in this compound and its derivatives as an aid to the study of biologic activity[5, 6].

It seems but a logical step to apply tetrazolium salt to the study of bacteria, particularly in those strains that are susceptible to suspension for vaccination. To determine the ratio of viable to dead bacillary bodies in the preparation is an important adjunct, as witnessed by the following quotation:

> ". . . it is pertinent . . . that investigators who are working in the preparation of B. C. G., or any other attenuated mycobacterium which may be used for vaccination purposes in humans, should have a fundamental knowledge of the viability of the microorganisms in order to assure vaccines of standard quality"[7].

This is especially important in view of the fact that BCG, as dispensed to date, must be administered with little knowledge concerning the viability of a given preparation.

The present technique of determining viability by colony counts has many recognized disadvantages. This, in addition to the advantages accruing from a method for rapidly determining the degree of viability in the various strains of BCG and R1Rv used for animal inoculation, has led to the investigation of the possibility of a rapid viability test.

Will viable tubercle bacilli absorb and reduce the tetrazolium salt while killed tubercle bacilli fail to so react? Experiments have been set up to determine these points and also to ascertain whether colorimetric determination of the degree of this reduction could be plotted as an essentially straightline curve on semi-logarithmic paper when varying concentrations of living and dead bacilli were employed. The following procedure has produced such evidence.

Two strains of tubercle bacilli were used, namely, BCG (Phipps) and R1Rv, and each was treated as indicated below. Approximately 20 mg. per ml. of an eight-day culture grown in Dubos albumin medium with 0.02 per cent Tween 80[8] was used. The concentra-

[1] This work was made possible through a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

[2] KUHN, R., AND JERCHEL, D.: Ber. deut. chem. Ges., 1941, *74*, 949.

[3] MATTSON, A. M., JENSEN, C. O., AND DUTCHER, R. A.: Science, 1947, *106*, 295.

[4] FRED, R. B., AND KNIGHT, S. C.: Science, 1949, *109*, 169.

[5] SMITH, F. E.: Science, 1951, *113*, 715.

[6] MUDD, S., WINTERSCHIED, L. C., DELAMATER, E. D., AND HENDERSON, H. J.: J. Bact., 1951, *62*, 459.

[7] STEENKEN, W., JR.: Am. Rev. Tuberc., 1950, *62*, 22.

[8] Tween 80 is the proprietary name for polyoxyethylene derivative of Sorbitan mono oleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

tions were determined nephelometricly. One half of the resulting suspensions of each strain was killed by flowing steam; the other half was maintained as a "live" vaccine. Dilutions were made using the "live" and dead suspensions in varying proportions so that successive tubes contained a decreasing proportion of living culture, the range in tubes passing from approximately 20 mg. per ml. "live" and no dead to no "live" bacilli and approximately 20 mg. per ml. killed bacilli. Each tube had the same final concentration, determined nephelometricly.

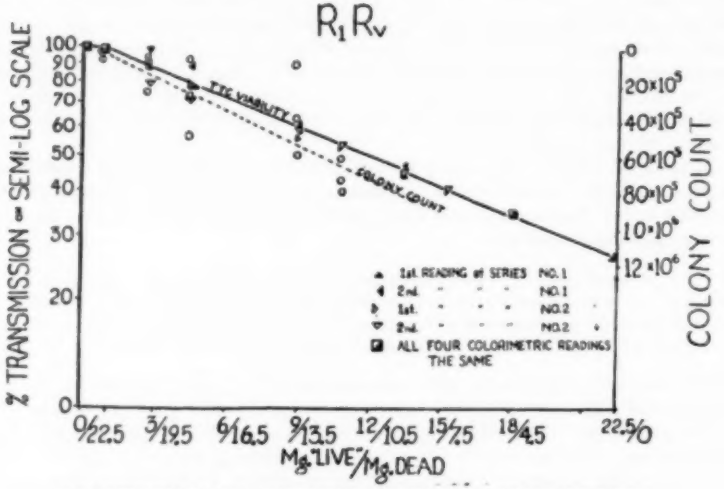

FIG. 1. The reduction of 2, 3, 5 triphenyltetrazolium chloride to red formazan by the biologic activity of varying concentrations (0 to 22.5 mg. per ml.) of "living" and dead tubercle bacilli (R1Rv), as indicated by the percentage transmission; this is plotted on semi-logarithmic graph paper. The trend of colony counts is plotted on regular graph paper.

At this stage two sets of observations were made to obtain the data shown in figure 1.

Procedure for colony determination: Each tube had sufficient suspension removed for colony counts. This suspension was divided and diluted serially. Each tube had at least four separate colony counts on four or more tubes of Löwenstein (Jensen)[9] medium inoculated from each dilution.

Procedure for colorimetric determination: One milliliter remained in each original tube after planting for colony count. These bacilli were washed and the supernatant fluid removed. To the centrifugalized sediment was added 1 ml. of an 0.25 per cent 2,3,5 triphenyltetrazolium chloride solution contained in Dubos basal medium[10] with 0.02 per cent Tween 80, 0.5 per cent glucose, and adjusted to pH 7.2. This was incubated at 37.5°C. for two hours. The tubes were taken from the incubator, 3.5 ml. of acetone

[9] HOLM, J., AND LESTER, V.: Acta tuberc. Scandinav., 1941, *16*, 3; abstracted, Pub. Health Rep., 1947, *62*, 847.

[10] DUBOS, R. J., AND FENNER, F.: J. Exper. Med., 1950, *91*, 261.

(Merck, N. F.) were added to each and agitated vigorously to extract the dye bound in the bacillary body. The suspensions were further diluted with 11.5 ml. of acetone in order to bring the range of color within the proper range of the colorimeter scale. The tubes were centrifugalized at 3,000 r.p.m. for fifteen minutes. The extracted color was read on a Bausch and Lomb Monochromatic Colorimeter using a 550 mμ filter and the B & L cuvettes.

The above procedure was not satisfactory for low concentration. Therefore, in determining the viability curve for low concentrations (0 to 4 mg. per ml.), the suspensions were

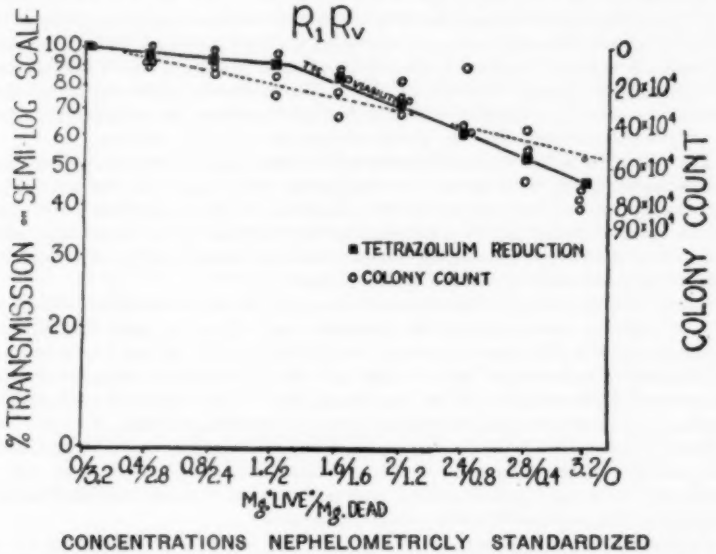

FIG. 2. The reduction of 2, 3, 5 triphenyltetrazolium chloride to red formasan by the biologic activity of weaker concentration (0 to 3.2 mg. per ml.) of living and dead tubercle bacilli (R1 Rv), as indicated by percentage transmission. Lower transmission reading is due to less dilution of dye before reading. The trend of colony counts is plotted on regular graph paper.

not diluted further after the original 3.5 ml. of acetone were added for extraction. Otherwise, the procedure was the same.

Color changes: The tubes containing living bacilli developed a deep red color, whereas those at the other end of the scale and containing killed bacilli remained entirely colorless. There was a gradual variation in the extent of color, a variation from tube to tube that was not always perceptible to the eye but was easily determined on the colorimeter and was very obvious in the entire series of tubes.

Colony counts: The colony counts obtained by serial dilution and planting on Löwenstein (Jensen) medium has demonstrated a decrease in colonies as the colorimeter has given an increase in transmission. Each circle on the curve (figure 1) represents the average of four counts made on that dilution. The colony counts were made before centrifugalizing and are representative of the viable units produced in the medium (Dubos with albumin

and 0.02 per cent Tween) used. No attempts were made to break up the clumps more than was inherent in the medium, but this point is being investigated at present. The dotted line represents the colony count trend.

Projection on curves: The readings that resulted were plotted on semi-log graph paper and gave the essentially straight line curve shown in figure 1. In these concentrations the graph demonstrates the percentage of "viable" cells to be a function of the degree of reduction of tetrazolium salt.[11] Series 1 represents tubes tested in the early morning and Series 2 represents those tested in the late afternoon. It is interesting to note how the two series coincide.

An interesting observation developed in the course of this work that is worthy of the following remark: The early and regular counting of colonies and their photogenicity can be materially enhanced by flooding the surface with 0.01 to 0.25 per cent Neotetrazolium chloride and placing in an incubator at 37.5°C. The incubation period may be varied in accordance with the intensity of coloration desired. Neotetrazolium added to the media in low concentration will allow the growth of dark blue or purple colonies.

The data given in figure 1 are within the colorimetric range of error for concentrations of 0 to approximately 2 mg. per ml. By reducing the diluent (acetone), one can increase the concentration of dye and increase the sensitivity of the test for this lower range. Figure 2 indicates the range of approximately 1.2 to 3.2 mg. per ml. to be satisfactory with this method. Again the average colony counts are represented by circles, with the dotted line representing the trend of colony counts.

A break is demonstrable at approximately 1 mg. in both of these graphs and has been so in all viability curves made in this laboratory with tetrazolium salt. At present no explanation of this phenomenon is known. Serial dilution of the reduced tetrazolium salt will not produce such a break, but a straight line curve is manifested from approximately 25 per cent transmission to 100 per cent transmission. This is regarded as possibly of fundamental importance, and efforts are under way toward its solution.

Streptomycin added to suspensions of tubercle bacilli sensitive to this drug inhibits this reduction of tetrazolium salt. In view of these preliminary observations, work is under way to develop a technique for a more rapid method of ascertaining streptomycin sensitivity, using some of the principles presented here.

Further studies are in progress to evaluate and improve these procedures and will be subsequently presented in a more detailed report.

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[11] It is necessary that the exposure to light be kept to a minimum, because such exposure will cause a change in the color of the salt and thus lead to false interpretation.

A TEST TUBE MODIFICATION OF THE OXIDATION-REDUCTION DYE TEST FOR THE DETERMINATION OF VIRULENCE OF MYCOBACTERIA IN VITRO

The oxidation-reduction dye test for the determination of virulence of *Mycobacteria in vitro* as developed in this laboratory (Wilson, F. J., Kalish, C., and Fish, C. H.: Am. Rev. Tuberc., 1952, *65*, 187) has recently been modified in order to reduce possible hazard to laboratory personnel. It has been found possible to substitute small test tubes (75 mm. by 10 mm.) for the porcelain spot plates originally described. Results can be obtained just as rapidly and in a much safer manner.

Five drops of the test dyes are placed in cotton-stoppered tubes by means of a capillary pipette, and a spade full of organisms is added. The tubes are placed in a test tube rack, shaken vigorously, and examined at the end of fifteen minutes against a white background.

Fifty-five additional pure cultures of *Mycobacteria* have been tested with this modified technique. Forty-eight of these did not reduce the dyes and were found to produce typical generalized tuberculosis in guinea pigs. The remaining seven cultures reduced the dyes and produced either no involvement or only slightly enlarged iliac and inguinal lymph nodes when 5 mg. was inoculated subcutaneously into guinea pigs. Seventy-five cultures were also tested which had recently been isolated from sputum and had been diagnosed as *Mycobacterium tuberculosis* on the basis of colonial characteristics. None of these organisms reduced the dyes.

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March 28, 1952

THE EFFECTS OF BARBITURATES ON THE TOXICITY OF ISONIAZID (ISONICOTINIC ACID HYDRAZIDE)

Isoniazid (isonicotinic acid hydrazide) has recently been reported effective in the chemotherapy of tuberculosis. Clinical reports by Robitzek and Selikoff (Am. Rev. Tuberc., 1952, *65*, 402), and Selikoff and Robitzek (Dis. of Chest, 1952, *22*, 385), have indicated, however, that a certain percentage of cases under treatment with this compound showed symptoms of toxicity indicative of central nervous system stimulation. The most frequently seen toxic symptoms were hyper-reflexia of deep reflexes, twitching of legs, vertigo, insomnia, et cetera.

Studies on the acute toxicity of isoniazid, conducted in this laboratory, also indicate that the drug is capable of exerting a very potent central nervous system stimulating action. It exhibits the same degree of toxicity in mice, whether given orally, subcutaneously, or intravenously.

The acute LD_{50} and 19/20 confidence limits following the various routes of administration of isoniazid are shown in table 1.

Immediately and up to twenty to thirty minutes following the administration of a lethal dose of isoniazid, the animals all appeared normal. The animals then began to show symptoms of central nervous system stimulation, such as excitement and running movements, which invariably ended in a series of clonic and tonic convulsions. The mice usually recovered from the first two or three seizures, but they all died of respiratory failure subsequent to a series of seizures. Death occurred within ten to thirty minutes after the onset of seizures, depending on the size of the dose given.

In view of the fact that the acute toxic manifestations following the administration of isoniazid are chiefly those of central nervous system stimulation, it appeared worth while to investigate whether or not the concurrent administration of barbiturates would lessen significantly these toxic effects. The results of preliminary studies on the effect of sodium pentobarbital and sodium phenobarbital upon the acute and chronic toxicity of isoniazid in mice and dogs are recorded in the present communication.

Effect of phenobarbital or pentobarbital on the toxicity of isoniazid in mice: Albino Swiss mice weighing 19 to 21 gm. were used. Each animal was given oraliy a dose of 250 mg. of isoniazid per kg. of body weight. This dose was predetermined to cause convulsions and death in 100 per cent of the mice. Phenobarbital or pentobarbital were given orally or subcutaneously. When given orally, they were given with isoniazid in the same solution; when given subcutaneously, they were given immediately following the oral dose of isoniazid.

All mice were observed closely during the first three hours and several times a day thereafter for three days. The time of onset of toxic symptoms, e.g., excitement, convulsions, and also of death were recorded.

The doses administered, as well as the convulsion and mortality rates of the mice which received isoniazid alone and of those which received isoniazid and barbiturates, are given in table 2.

An analysis of the results shown in table 2 indicates that both pentobarbital and phenobarbital are able to protect mice from convulsive and lethal doses of isoniazid. Animals receiving isoniazid and pentobarbital usually were preceded by a short period of depression which lasted ten to twenty minutes. Such phenomena were not observed, however, in mice which received isoniazid and phenobarbital. These differences may be accounted for by the difference in the times of maximal actions of isoniazid, pentobarbital,

and phenobarbital. It is to be remembered that pentobarbital is a quick-acting, whereas phenobarbital is a slow-acting, barbiturate. The maximal action for the former is usually

TABLE I

ACUTE TOXICITY OF ISONIAZID IN MICE

ROUTE OF ADMINISTRATION	NUMBER OF MICE	LD_{50} (19/20 CONFIDENCE LIMITS)	
		mg/kg mouse	
Oral	60	170	(165–175)
Subcutaneous	60	150	(120–160)
Intravenous	156	165	(155–170)

TABLE 2

ANTIDOTAL EFFECT OF PENTOBARBITAL AND PHENOBARBITAL ON THE ACUTE TOXICITY OF ISONIAZID IN MICE

ISONIAZID		PENTOBARBITAL		PHENOBARBITAL		CONVULSION RATIO*	MORTALITY RATIO*
Dosage	Route	Dosage	Route	Dosage	ROUTE		
mg/kg		*mg/kg*		*mg/kg*			
250	Oral	50	Oral			5/10	0/10
250	Oral	40	Oral			10/10	1/10
250	Oral	30	Oral			10/10	6/10
250	Oral	50	Subcutaneous			0/10	0/10
250	Oral	40	Subcutaneous			0/10	0/10
250	Oral	30	Subcutaneous			1/10	2/10
250	Oral	0 (Control)				10/10	10/10
250	Oral			150	Oral	0/10	0/10
250	Oral			100	Oral	5/10	1/10
250	Oral			50	Oral	10/10	2/10
250	Oral			25	Oral	10/10	7/10
250	Oral			150	Subcutaneous	0/10	0/10
250	Oral			100	Subcutaneous	5/10	0/10
250	Oral			50	Subcutaneous	10/10	3/10
250	Oral			25	Subcutaneous	5/5	2/5
250	Oral			0 (Control)		10/10	10/10

* The ratio of the number of mice that had convulsions or died to the number of animals used in the group.

reached within ten minutes and that for the latter is reached in thirty to fifty minutes. The maximal convulsant action of isoniazid is reached also in thirty to fifty minutes. The coincidence of the maximal actions of isoniazid and phenobarbital therefore makes phenobarbital a more suitable antidote for isoniazid than pentobarbital.

Effect of phenobarbital on the toxicity of isoniazid in dogs: Four female mongrel dogs

weighing 5.7 to 8.1 kg. were used. The animals were divided into two groups. *Group I* consisted of 2 dogs, each of which received daily 40 mg. of isoniazid per kg. of body weight. *Group II* consisted of 2 dogs, each of which received 40 mg. of isoniazid and 5 to 10 mg. of sodium phenobarbital per kg. of body weight per day. Both isoniazid and phenobarbital were given orally by stomach tube.

It will be noted from table 3 that dogs Nos. 267 and 263, which received 40 mg. of isoniazid per kg. per day, manifested their first attacks of convulsive seizures on the first and fourth days, respectively, of the experiment and frequently thereafter. The seizures consisted of a series of clonic and tonic convulsions, during which time the animals were very much prostrated. Each of these attacks lasted sixty to ninety minutes, after which the animal recovered but remained in a state of prostration for several more hours.

TABLE 3

EFFECT OF PHENOBARBITAL ON THE TOXICITY OF ISONIAZID IN DOGS

DOG NUMBER	ISONIAZID mg/kg/day (Oral)	SODIUM PHENOBARBITAL mg/kg/day (Oral)	TOXIC SYMPTOMS
267	40	0	This dog had a series of tonic and clonic convulsive seizures on the first, fourth, seventh, ninth, and eleventh days of administration. Died on the eleventh day during the height of seizures.
263	40	0	This dog had convulsive seizures on the fourth, eighth, tenth, and eleventh days of isoniazid administration. Died on the eleventh day during the height of convulsive seizures.
266	40	10	No convulsions for seven days. Dog was found dead on the seventh day. At autopsy it was found that this dog had swallowed a large piece of cotton. A cotton ball, the size of a large apple, was found in the stomach and duodenum.
271	40	5	No convulsions during a two-week period. This dog is still receiving daily doses of isoniazid and phenobarbital.

Both dogs died on the eleventh day. On several occasions when these dogs developed convulsive seizures, they were given, intravenously, 5 to 10 mg. of pentobarbital or phenobarbital per kg. of body weight. Pentobarbital was found to be more effective than phenobarbital, and the convulsive seizures ceased before injection of the barbiturate was completed.

Dog. No. 266 received daily 40 mg. of isoniazid and 10 mg. of phenobarbital per kg. No convulsive seizures developed for as long as seven days. Unfortunately, this dog died on the seventh day of intestinal obstruction. At autopsy there was found a big lump of cotton, the size of a large apple, in the stomach and duodenum. Dog. No. 271 received daily 40 mg. of isoniazid and during the first week 10 mg. of phenobarbital per kg. and thereafter the same amount of isoniazid with 5 mg. of phenobarbital. This animal had no convulsive seizure during a course of two weeks.

From the experiments with mice and dogs described above, it is evident that phenobarbital or pentobarbital are able to protect animals against isoniazid convulsions and death. The antagonistic effect of the barbiturates against the central nervous system stimulating effect of isoniazid suggests that, in patients receiving isoniazid treatment

and manifesting symptoms suggestive of central stimulation, such as hyper-reflexia, leg twitching, insomnia, et cetera, phenobarbital administered in small doses simultaneously with isoniazid may be of help in preventing these symptoms. For reasons discussed above, phenobarbital would seem to be a more suitable antidote for isoniazid than pentobarbital.

In summary: In toxic doses, isoniazid manifests in experimental animals symptoms of central nervous system stimulation. The simultaneous administration of small doses of barbiturates was found to be able to antagonize these toxic symptoms. Phenobarbital is preferred over pentobarbital in that the maximal action of both isoniazid and phenobarbital are reached at approximately the same time. It is suggested, therefore, that small doses of phenobarbital may be of benefit in preventing or alleviating the toxic symptoms due to central stimulation in patients receiving isoniazid therapy.

For immediate or quick relief of acute toxic symptoms of central stimulation after they had manifested themselves, pentobarbital should be preferred over phenobarbital because the former is quick acting and reaches its maximal action much faster than the latter.

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Medical Section of the National Tuberculosis Association

Report on Projects for the Recovering Tuberculosis Patient in Some European Countries

The following observations on rehabilitation of tuberculous patients in some European countries were the result of a tour undertaken in April, May, and June of 1951. The chief objective was to ascertain what items in European practice might be applicable to American needs. The countries visited were Holland, Western Germany, Switzerland, Denmark, Sweden, Finland, Norway, England, and Scotland. Not all of the rehabilitation was seen, but an attempt was made to view some characteristic projects in each country for recovering tuberculosis patients.

One general conclusion by this observer is that, despite the fact that current vocational rehabilitation in the United States still falls far short of meeting even a substantial portion of patient needs, the growth of rehabilitation as an item of tuberculosis control is more generally distributed within the United States than in any European area. All of our states serve some few of the many patients needing vocational rehabilitation; some serve hundreds every year of the thousands needing service; most of the states reach patients at considerable distances from metropolitan areas. European rehabilitation is rarely available throughout a nation, even when well developed in a metropolis. On the other hand, some problems of the chronic patient have been attacked with more candor, more vigor, and more resources in Europe than is general throughout the United States.

HOLLAND

Two projects in Holland are pioneer undertakings both chronologically and idealogically. Berg en Bosch Sanatorium is a projection of the planning of Professor Bronkhorst although he is no longer active in its direction. Something not often seen in American institutions is landscaping so planned that each patient looks out upon an attractive garden scene which exists *for him* and not for visitors or politicians. When he has turned the corner clinically toward recovery, exercise is available in the form of toy construction. The toys are attractively designed, standardized articles with well-organized marketing channels in various European cities. The patient is encouraged to learn all of the processes which go into the making of the toys.

For patients whose needs are not met by this project, alternative occupations and instruction are available. A patient may, when medically authorized, undertake academic or vocational studies, learn bookbinding or more general applications of woodworking than toymaking.

A somewhat different program is operated at Zonnestraal Sanatorium near Hilversum. Its population is made up of industrial workers or members of their families, and every effort is made to refresh and upgrade the industrial skills of the recovering patient. The equipment of the institution includes substantially equipped metal and woodworking shops. These are operated with patients whose physical activity is medically prescribed and is advanced gradually until the patient is ready for normal employment with only periodic medical supervision. Much of the shop output consists of light assembly work on subcontracts obtained from electrical and other industrial concerns.

Another feature (also observed with variations in Sweden, Finland, and Great Britain)

consists of domiciliary provisions for patients who continue to have, either intermittently or persistently, sputum positive for tubercle bacilli after receiving maximum hospital benefits. Some of them are housed with their families; some are employed within the institution; some in the community; all at tasks whose selection is medically controlled. Some are reported finally to have sputum consistently negative for tubercle bacilli; all are reported to do better clinically while employed than is usual with idle patients in the same category. Some patients earn all, and some a part, of their living budgets. Only acutely ill patients occupy beds operated by infirmary standards in this institution.

A third project visited, Het Nederlands Studenten Sanatorium, is smaller in size and has been in operation but two years. The current census was twenty-three, but building construction was in progress to increase the capacity to eighty-five. It is a sanatorium for students at the university level of education. Its patients have been referred by Dutch universities. Priority has been given to applicants who are faced with the need for a long course of treatment; minimal cases are seldom admitted. Present facilities are relatively simple; surgical and major medical aid are available from an adjacent general sanatorium. Here the rehabilitation consists in the advancement of the patients' academic program under medical prescription. The pace of study is controlled by clinical considerations. Faculty is co-opted from various Dutch universities; distances in this country are inconsiderable. Instruction is necessarily primarily individual.

This project is a frank adaptation of a Swiss scheme to Dutch needs. One skeptical Dutch clinician wonders whether the supply of tuberculous students in Holland will continue to be as large as during the two years in which this project has operated to its present capacity.

Possibly as significant to the future of the Dutch patient as these institutional projects is a special staffing in Amsterdam by the Labor Ministry for the training and placement in industry of disabled persons, including the tuberculous. This staffing includes medical personnel, counselors, and training officers, all familiar with the rehabilitation literature of other nations and in frequent contact with the treatment institutions of their country.

OCCUPIED GERMANY

Projects visited in Occupied Germany were operated by the International Refugee Organization in the United States and French occupied zones. They consisted of an 800-bed sanatorium at Gauting, near Munich, and rehabilitation centers for tuberculosis patients at Lindich, not far from Stuttgart, and at Luttensee near the Austrian border. Gauting had some 800 patients under infirmary treatment; the census of Lindich was 110; that of Luttensee, 295 ambulant patients.

The teamwork between staff members of different national origins which made up the performance of International Refugee Organization treatment and rehabilitation units surpassed a great deal of what goes on in the individual nations from which personnel was recruited.

At Gauting, for example, a British-trained occupational therapist had been able to make the service of her staff a definitely therapeutic program prescribed by physicians of several nationalities. Procedures in all three projects were planned around the axiom that a displaced person who has had tuberculosis can seldom be resettled on the basis of his disability; generally, it is his abilities and skills which unlock the gates for him. Hence, throughout diagnostic and treatment procedures, as well as at rehabilitation centers, the search for latent aptitudes, experience, and skills was continuous and universal. Patients were promoted from sanatoriums to rehabilitation centers when, in the opinion of medical staff, they were ready for graduated exercise and training for employment.

The two rehabilitation centers visited were staffed with full-time physicians, nurses, technicians, counselors, instructors, and social workers. The equipment for training was comparable with that of average technical schools in the United States. Lindich (in the French zone), while the smaller of the units observed, had the unique experience of placing a number of DP's in the German economy with official work permits because they had been trained in a skill which was in short supply there. The location of Lindich near industrial centers was apparently a contributory factor. Luttensee (in the United States zone), beautifully but impractically situated near the Tyrol, had to rely entirely upon resettlement, usually in the Western hemisphere, i.e., Australia, Central and South Americas, Canada, and occasionally the United States.

The training objectives in these centers included woodworking, lighter forms of metal working, radio circuits, mechanical drafting, horology, and precision instruments, and, for some patients with optimum prognosis, a program of horticulture. Interruptions of program by reason of tuberculosis reactivation were reported not to exceed 10 per cent of enrollment.

Further reference to Switzerland and Denmark are omitted from this report because this reporter saw in neither nation rehabilitation projects of probable interest to readers of the REVIEW.

SWEDEN

Tuberculosis control in Sweden has earned a world-wide reputation for emphasis on discovery, but is now increasing its emphasis on recovery. In particular, the Central Chest Clinic of Stockholm sponsors a series of convalescent homes for tuberculous patients who have reached an ambulant stage. Each of these homes is staffed with a matron, one or more nurses (according to census), an occupational therapist, a maintenance man, a dietitian, a kitchen staff, a visiting physician. The cost per patient per day is, as might be expected, one-fifth of that of hospital care of the infirmary type. Other considerations, however, loom larger than costs. Patients whose work habits have deteriorated during absolute bed rest are required to undertake individual responsibilities for the operation of the unit in which they live. Part of the responsibility of the physician is to review and affirm these assignments on a prescription basis, to be put in effect by the extra-clinical staff.

The occupational therapist studies the experiences, skills, and aptitudes of each patient and, as recovery progresses, introduces assignments which brush up old skills or help to prepare for new ones. Administrators may be interested in the fact that coeducational convalescent homes are reported to have a more satisfactory morale than have the celibate units, without notable increase in disciplinary problems.

The convalescent homes are for the generality of ambulant patients and include some chronic cases as well as patients for whom treatment has yielded more satisfactory results.

The Stockholm Central Clinic also sponsors a small factory where assembly processes in telephony and radio are done on a subcontract basis. This unit provides a center for part-time employment and also provides jobs for a number of chronic patients who do as well or better while at work but who should not be presently employed without medical supervision. Between the two facilities the location and condition of chronic patients are known and their opportunities to infect others are minimized.

The records of the Central Clinic in Stockholm are rewarding to the statistically minded and may before long prove an instrument for some valuable clinical and social research.

FINLAND

Bed shortages in Finland have to be endured because the resources of the country are strained to pay off ferocious reparations which are collected as a consequence of World War II. Hence, like the Swedish, they use their tuberculosis hospital beds for the acutely

ill and improvise convalescent homes out of some of the larger farmhouses and other available buildings. The growth of such projects has been a gradual and evolutionary process and formal organization is not yet in evidence.

An organization of disabled veterans stepped into a pioneer role in vocational rehabilitation of the tuberculous, beginning with veterans of World War II. Setting up a training campus at Liperi which would do credit to a state college in this country, they organized a two-year trade training course for medically selected veterans, featuring mechanical and electrical instruction. This project has enjoyed governmental subsidy. As the number of tuberculous veterans decreases, patients without military history are accepted for training and may, in time, constitute the entire census.

NORWAY

Norwegian tuberculosis workers were fairly unanimous in the opinion that they were merely beginning effective work in the field of rehabilitation for the tuberculous. In Oslo, a rehabilitation center has been established which is devoted chiefly to tuberculosis because that is the principal physical disability. Patients are admitted and studied for a two-week stay, medically, socially, and in terms of potential employment. The resident staff appeared to be well equipped in terms of training and experience and was making the most of modest facilities.

At Krokeide, outside of Bergen, a tuberculosis rehabilitation training center is operated with some governmental subsidy by a patients' organization. The present census is fifty; the period of training, ten months; the courses, woodworking, precision metal working, electrical work, radar (especially radar and ships' radio).

Several small-shop projects in Oslo were visited which proved to be of the subcontract type, providing employment on a part-time basis but with little organized training.

GREAT BRITAIN

On visiting Papworth Village Settlement, a pioneer venture of its kind in Great Britain, it is easy to realize at once why a number of American visitors have been so deeply impressed. After thirty years of operation and the application of many bequests, it has grown into a very sightly village of 2,000 persons. Its several industries, with an annual output exceeding 492,000 British pounds, are equipped with more modern automatic machinery than is usual in Britain's commercial industries. This part of the project is served by an imaginative and aggressive sales department. Currently, the factories make quality luggage, incubators, furniture, station wagon auto bodies, and printed matter. Employment is medically prescribed; the quality of output is marketable at top prices; patient labor is supplemented by workers without medical history on the more exhausting jobs. The central theme of this project has been permanent settlement in medically supervised employment. Applicants willing to entertain such plans, at least tentatively, have had priority up to the election of a National Labor Government. Recently, the Health Ministry has required the acceptance of 100 patients annually who were interested in rehabilitation but not necessarily in settlement.

The major tangible and unique features are the thriving industries and the permanent housing for all types of colonists and their families. Another unique feature is the complete medical care of all colonists through the operation of a daily outpatient clinic supplemented by house visits made by members of the medical staff.

Earlier housing for unattached individuals included numerous small huts. The management has found these increasingly expensive to maintain and newer construction is of the miniature apartment type. Family housing is available in a variety of forms which include duplex houses, small apartment quarters, and single detached houses. A substantial portion of the construction is conducted by former patients who have been medically

certified and who have the requisite skills, while the heavier work is performed by persons without history of tuberculosis.

Papworth Village Settlement has supplied precedent and demonstration which are acknowledged by personnel in many other projects throughout Great Britain. However, variations have been developed to meet local situations, differences in available resources, and concepts of method most effective for the area and patients involved. The chief point of departure is opposition to the theme of permanent settlement or of large projects at a distance from the previous homes of the patients. Among smaller projects visited was Preston Hall, in Kent, infirmary center for the British Legion Industries. It is a smaller project; its output is in simpler articles (for example, hen houses, stock feeders, et cetera); patient turnover is encouraged. Preston Hall seeks local rather than export markets.

In an irregular pattern in the west of England lie boroughs and counties containing small sanatoriums, small patient villages, small shops. They use adaptations of the settlement pattern for patients with unstable lesions; feed employable patients into the projects of the National Labor Ministry.

Five of the chain of the government-sponsored Remploy Shops operated throughout the United Kingdom for disabled persons were visited. The chain represents an attempt by the government to offset the general hostility of British employers toward disabled persons through interim employment under medical direction. A few shops are for individual disabilities, such as tuberculosis; the majority are for a mixture of recovered patients. In some five years of operation, uniformity of standards is an aspiration more often than an achievement. An attempt is made to vary the industries to the needs, resources, and markets of the area. Near London the emphasis is on light articles of furniture; in the West some of the shops produce farm supplies (for example, potato boxes); in Birmingham, electrical fans are assembled; and, in Scotland, articles of furniture are currently the chief product. Production is reported to correlate considerably with the attitudes acquired by patients during hospitalization. In the London area, absenteeism runs high; in Scotland, it is reported a negligible problem.

In attempting to lessen the growing pains of this effort, cooperation is developing with health, labor, and welfare agencies so that preliminary reorientation to work habits precede actual employment in production, and medical re-check is available at each step.

Unique features in these enterprises are the responsibility assumed by official agencies and the effort to make facilities available where needed throughout the United Kingdom.

COMMENT

With few exceptions, European tuberculosis workers voiced the conviction that in the study and practice of programs for lasting recovery the United States is today's pioneer, save in some specific items. It is apparent that they are more aware of published reports of work methods and accomplishments than of our fragmentary studies of unmet needs.

In most of the countries visited, extra-clinical personnel with training apposite to their responsibilities is scanty or nonexistent. For all the obstacles still encountered here in the adjustment, stabilization, training, and placement of the handicapped, none of these nations has a comparable experience in employing disabled workers, nor as general an acceptance of their capacity for production. The range of occupations available to disabled persons in these countries is generally far smaller than in much of the United States.

None the less, the projects noted in these pages are informing and of substantial value to any American observer interested in recovery measures, if only as reassurance concerning domestic efforts. The best of them in each country are clearly attempts to make the most practical application of available resources in such a way as to serve outstanding needs of the patients and the area concerned.

HOLLAND HUDSON

Tuberculosis Mortality Among Residents of Large Cities (1947–1949)

This analysis of tuberculosis mortality among residents of large cities, based on data compiled by the Bureau of the Census and the National Office of Vital Statistics, represents the first tabulation of urban mortality which has been available in the United States since 1941. During the past decade, the extensive civilian and military migration in all sections of the country, which was occasioned by World War II and its aftermath, made it impossible to estimate the population in cities with any degree of accuracy. With the publication of 1950 census data, the necessary population estimates on which death rates are based can readily be computed.

In assembling mortality data for American cities, a three-year basis was decided upon as a means of minimizing the chance fluctuation incident to small numbers, and also as a means of minimizing certain minor changes in classification first followed in 1949. Accordingly, annual average tuberculosis death rates were computed for the three-year period 1947–1949; these are the most recent years for which mortality figures are available. The population base on which these average death rates were figured is the estimated population for July 1, 1948, the mid-point of the three-year period.

According to the Census of 1950, the United States had 106 cities of 100,000 population or more. For the purposes of this study these 106 cities have been divided into four groups: 18 cities of 500,000 or more in 1950; 23 with 250,000 but less than 500,000 population in 1950; 50 cities of 100,000 but less than 250,000 population both in 1950 and in 1940; and 15 cities whose population was 100,000 or more in 1950 but less than that in 1940.

A similar analysis of mortality data, based on the three-year period, 1939–1941, was published in *Public Health Reports* on July 21, 1944. This article, entitled "Tuberculosis Mortality Among Residents of the 92 Cities[1] of 100,000 or More Population: United States, 1939–1941" by Dorothy J. Liveright, serves as the basis of comparison for the findings in this study. The enumerated population according to the Census of 1940 was used as the basis for mortality rates listed in Mrs. Liveright's article.

Variation in death rates by size of community: During 1947–1949 the tuberculosis death rate was highest in the largest cities and showed a somewhat regular decline in the next two population categories. In the 18 cities with a population of 500,000 or more in 1950, the average mortality rate was 42.9 per 100,000, compared with a rate of 29.6 for the country as a whole. In other words, tuberculosis is primarily a disease of large cities although the disease exists, sometimes unrecognized, in communities of every size and type. In view of the crowded living conditions in many of our large cities, it is not surprising that this communicable disease is most prevalent in these populous communities.

Table 1 shows the average annual tuberculosis death rates for the three-year period, 1947–1949, classified by cities of the four different population groups, compared with similar information for 1939–1941. In addition, the percentage of decline in the mortality rates from the earlier to the later period appears in this table.

Not only is the tuberculosis death rate highest in the 18 most populous cities, but the rate for 1947–1949 has declined less in the preceding eight years than the rate for any other group of urban communities. In the most recent period studied, the death rate in the largest cities is 17 per cent more than that for cities of the next largest category, while eight years earlier the corresponding figure was but 2 per cent.

Cities with 500,000 population or more in 1950: A wide range was noted in the tuberculosis mortality for these 18 large cities as shown in table 2.

[1] In the Census of 1940, Lowell, Massachusetts, had a population of 101,389; in 1950, this city, with a population of 97,249, dropped out of the 100,000 category.

TABLE 1

AVERAGE ANNUAL TUBERCULOSIS DEATH RATES AND PERCENTAGE OF DECLINE IN RATES, CLASSIFIED BY CITIES GROUPED ACCORDING TO POPULATION IN 1950: UNITED STATES, 1947–1949 AND 1939–1941

POPULATION GROUP IN 1950	NUMBER OF CITIES STUDIED	AVERAGE ANNUAL TUBERCULOSIS DEATH RATE		PERCENTAGE OF DECLINE IN DEATH RATE
		1947–1949	1939–1941	
United States	106	29.6	45.9	35.5
Cities of 500,000 and over	18	42.9	57.7	25.6
Cities of 250,000 to 500,000	23	36.7	56.4	34.9
Cities of 100,000 to 250,000*	50	31.6	46.5	32.0
Cities of 100,000 to 250,000†	15	41.6	82.0	49.3
Balance of country		25.4	41.5	38.8

* Both in 1950 and in 1940.

† In 1950, but less than 100,000 in 1940.

TABLE 2

TUBERCULOSIS MORTALITY AMONG RESIDENTS OF CITIES WITH 500,000 OR MORE POPULATION IN 1950: UNITED STATES, 1947–1949 AND 1939–1941

CITY	1947–1949			1939–1941		
	Estimated population July 1, 1948	Tuberculosis deaths		1940 population	Tuberculosis deaths	
		Average annual number	Average annual rate		Average annual number	Average annual rate
Total	26,172,001	11,228	42.9	24,194,856	13,959	57.7
Minneapolis, Minn.	516,582	102	19.7	492,370	103	20.9
Milwaukee, Wis.	628,656	161	25.6	587,472	231	39.3
Los Angeles, Cal.	1,888,794	676	35.8	1,504,277	836	55.6
St. Louis, Mo.	849,665	309	36.4	816,048	454	55.6
Houston, Texas	559,124	209	37.4	384,514	286	74.4
New York, N. Y.	7,815,489	3,028	38.7	7,454,995	3,836	51.5
Detroit, Mich.	1,809,998	764	42.2	1,623,452	823	50.7
Pittsburgh, Pa.	675,905	287	42.5	671,659	351	52.3
Buffalo, N. Y.	579,392	255	44.0	575,901	277	48.0
Cleveland, Ohio	908,425	412	45.4	878,336	534	60.8
Chicago, Ill.	3,581,735	1,632	45.6	3,396,808	2,119	62.4
Philadelphia, Pa.	2,047,058	961	46.9	1,931,334	1,258	65.1
San Francisco, Cal.	750,713	363	48.4	634,536	427	67.4
New Orleans, La.	557,161	295	52.9	494,537	400	81.0
Cincinnati, Ohio	495,530	263	53.1	455,610	306	67.2
Boston, Mass.	796,084	441	55.4	770,816	465	60.3
Washington, D. C.	777,838	459	59.0	663,091	548	82.7
Baltimore, Md.	933,852	611	65.4	859,100	705	82.1

Minneapolis, a city with a homogeneous population, with higher than average economic and educational levels, had an average death rate of 19.7 per 100,000 during 1947–1949. Eight years earlier the tuberculosis mortality in this city was likewise extremely low when compared with other metropolitan centers of similar size. Milwaukee, another city with a

favorable death rate in the more recent period, has made a pronounced improvement since 1939–1941.

Baltimore, on the other hand, had an average tuberculosis mortality rate of 65.4 in this recent study, compared with 82.1 eight years earlier. The corresponding rates for Washington, D.C., were 59.0 and 82.7, respectively. In these two cities large segments of the population are liable to have a high mortality from tuberculosis.

Houston, with a 55 per cent increase in its population during the past decade, has registered a 50 per cent decline in its tuberculosis death rate between the two periods studied.

In a few of our most crowded cities an opinion is growing to the effect that a significant change in population is rapidly taking place. In other words, families in fairly comfortable circumstances are being influenced to move from deteriorating apartments or homes to suburban areas because of overcrowding in the city's residential sections, heavy traffic, smoke nuisance, and allied evils. When the crowded sections thus left vacant are occupied by families of a lower economic and probably of a lower educational level, the city's tuberculosis death rate may be affected in two ways:

1. Those who move away represent a sector of the population among whom tuberculosis as a rule is not especially prevalent.
2. Those who move in are often peculiarly subject to the disease because of their less fortunate status.

Newcomers in the latter category may in addition comprise a racial group who are not only susceptible to tuberculosis, but who may be unfamiliar with the customs, the climate, and even the language prevailing in the city of their new residence.

If tuberculosis mortality data were available for the entire metropolitan areas of these crowded communities, instead of being limited to the cities proper, it is quite possible that more favorable death rates would be shown. In any case this peculiar situation probably affects the very largest cities only, those which no longer have within their limits pleasant residential sections and open spaces in which to expand.

Cities of 250,000 to 500,000 population in 1950: The tuberculosis death rate averaged 36.7 per 100,000 in the recent study of 23 cities classified in the group with 250,000 to 500,000 population. In 1939–1941 the corresponding rate for these cities was 56.4. The percentage of decline in the rate for 1947–1949, when compared with the rate eight years earlier, was 34.9—considerably higher than the percentage of decline in the rate for the largest cities as a group.

Among the 23 cities in the second population group, the tuberculosis mortality rate ranged from 14.4 per 100,000 in Long Beach, California, to 79.4 in San Antonio, Texas, according to table 3.

A striking feature of table 3 has to do with the number of these medium-sized cities in the West and South which have registered marked declines in tuberculosis mortality between the two periods studied. The most pronounced drop of all is noted for Memphis, Tennessee, where the average tuberculosis death rate in 1939–1941 had declined 64 per cent by 1947–1949.

Several California and Texas cities have had higher than average decreases in tuberculosis mortality, while during the past decade their population has increased at an astonishing rate.

An enormous population increase in a relatively short period often results in chaotic living conditions and the lack of proper health, welfare, and educational facilities. Since such shortcomings are concomitants of high tuberculosis mortality, it is surprising indeed to note these pronounced declines in the death rates of such rapidly growing cities.

TABLE 3

TUBERCULOSIS MORTALITY AMONG RESIDENTS OF CITIES WITH 250,000 TO 500,000 POPULATION IN 1950: UNITED STATES, 1947-1949 AND 1939-1941

CITY	1947-1949			1939-1941		
	Estimated population July 1, 1948	Tuberculosis deaths		1940 population	Tuberculosis deaths	
		Average annual number	Average annual rate		Average annual number	Average annual rate
Total	7,982,119	2,927	36.7	6,760,888	3,814	56.4
Long Beach, Cal.	235,630	34	14.4	164,271	44	26.6
St. Paul, Minn.	307,217	53	17.3	287,736	77	26.8
Akron, Ohio	269,388	55	20.4	244,791	61	25.1
Omaha, Neb.	246,344	59	24.0	223,844	78	34.9
San Diego, Cal.	311,454	77	24.7	203,341	95	46.9
Dallas, Texas	410,010	105	25.6	294,734	170	57.6
Fort Worth, Texas	261,083	69	26.4	177,662	85	47.8
Portland, Ore.	361,687	104	28.8	305,394	97	31.9
Denver, Colo.	399,446	119	29.8	322,412	176	54.7
Rochester, N. Y.	331,173	100	30.2	324,975	102	31.5
Seattle, Wash.	450,268	136	30.2	368,302	180	48.8
Memphis, Tenn.	377,965	122	32.3	292,942	261	89.1
Oakland, Cal.	370,153	127	34.3	302,163	122	40.5
Columbus, Ohio	363,684	126	34.6	306,087	171	55.8
Kansas City, Mo.	446,569	155	34.7	399,178	205	51.4
Indianapolis, Ind.	420,138	169	40.2	386,972	212	54.9
Jersey City, N. J.	299,017	136	45.5	301,173	171	56.8
Birmingham, Ala.	315,808	144	45.6	267,583	224	83.7
Toledo, Ohio	299,894	140	46.7	282,349	187	66.1
Atlanta, Ga.	326,234	165	50.6	302,288	261	86.5
Louisville, Ky.	360,370	192	53.3	319,077	170	53.4
Newark, N. J.	437,198	237	54.2	429,760	280	65.2
San Antonio, Texas	381,389	303	79.4	253,854	385	151.7

TABLE 4

PERCENTAGE INCREASE IN POPULATION BETWEEN 1940-1950 AND PERCENTAGE DECREASE IN TUBERCULOSIS MORTALITY BETWEEN 1939-1941 AND 1947-1949: SELECTED CALIFORNIA AND TEXAS CITIES

CITY	PERCENTAGE INCREASE IN POPULATION: 1940-1950	PERCENTAGE DECREASE IN TUBERCULOSIS MORTALITY: 1939-1941 TO 1947-1949
Dallas, Texas	47	56
Fort Worth, Texas	57	45
Long Beach, California	53	46
San Antonio, Texas	61	48
San Diego, California	64	47

Curiously enough, these large population increases, together with equally substantial decreases in tuberculosis mortality, are found not only for Long Beach, the city of this group with the lowest death rate in the recent period studied, but also for San Antonio, the community with the highest rate among cities of this size. The latter city has had for

TABLE 5

TUBERCULOSIS MORTALITY AMONG RESIDENTS OF CITIES WITH 100,000 TO 250,000 POPULATION BOTH IN 1950 AND IN 1940: UNITED STATES, 1947–1949 AND 1939–1941

CITY	1947–1949			1939–1941		
	Estimated population July 1, 1948	Tuberculosis deaths		1940 population	Tuberculosis deaths	
		Average annual number	Average annual rate		Average annual number	Average annual rate
Total	7,589,125	2,398	31.6	6,930,856	3,220	46.5
Wichita, Kan.	158,949	18	11.3	114,966	30	26.4
Salt Lake City, Utah	176,488	21	11.9	149,934	29	19.3
Duluth, Minn.	103,908	13	12.5	101,065	25	25.1
Des Moines, Iowa	174,789	26	14.9	159,819	36	22.7
Spokane, Wash.	154,770	24	15.5	122,001	29	23.8
Flint, Mich.	161,113	26	16.1	151,543	39	25.5
Grand Rapids, Mich.	174,376	30	17.2	164,292	26	15.6
Charlotte, N. C.	130,357	24	18.4	100,899	46	45.6
Peoria, Ill.	110,671	21	19.0	105,087	28	27.0
Oklahoma City, Okla.	236,665	48	20.3	204,424	80	39.0
South Bend, Ind.	113,348	23	20.3	101,268	37	36.9
Springfield, Mass.	160,151	35	21.9	149,554	41	27.2
Bridgeport, Conn.	156,681	36	23.0	147,121	57	38.5
Elizabeth, N. J.	112,309	26	23.2	109,912	44	40.0
Kansas City, Kan.	128,136	31	24.2	121,458	53	43.6
Canton, Ohio	115,423	28	24.3	108,401	44	40.6
Yonkers, N. Y.	151,013	37	24.5	142,598	54	37.6
Utica, N. Y.	101,354	25	24.7	100,518	31	30.8
Youngstown, Ohio	168,223	42	25.0	167,720	66	39.6
Somerville, Mass.	102,321	26	25.4	102,177	28	27.7
Tacoma, Wash.	137,677	37	26.9	109,408	44	40.2
Paterson, N. J.	139,336	38	27.3	139,656	45	32.2
New Haven, Conn.	163,771	45	27.5	160,605	53	33.0
Providence, R. I.	248,674	69	27.7	253,504	100	39.5
Tulsa, Okla.	175,638	50	28.5	142,157	95	67.1
Syracuse, N. Y.	218,025	63	28.9	205,967	66	32.0
Fort Wayne, Ind.	130,948	38	29.0	118,410	48	40.5
New Bedford, Mass.	109,189	32	29.3	110,341	55	50.1
Worcester, Mass.	201,772	62	30.7	193,694	69	35.[illegible]
Erie, Pa.	128,380	40	31.2	116,955	43	[illegible]
Cambridge, Mass.	119,014	38	31.9	110,879	54	48.4
Scranton, Pa.	125,536	42	33.5	140,404	56	39.7
Miami, Fla.	235,783	83	35.2	172,172	99	57.5
Reading, Pa.	109,320	41	37.5	110,568	56	50.4
Knoxville, Tenn.	122,461	46	37.6	111,580	69	62.1
Norfolk, Va.	201,406	78	38.7	144,332	116	80.6
Hartford, Conn.	175,449	68	38.8	166,267	60	36.1
Dayton, Ohio	238,070	93	39.1	210,718	142	67.4
Camden, N. J.	123,327	50	40.5	117,536	61	51.9
Gary, Ind.	130,027	53	40.8	111,719	74	66.2
Nashville, Tenn.	173,099	73	42.2	167,402	133	79.3
Trenton, N. J.	127,429	57	44.7	124,697	84	67.4
Wilmington, Del.	110,356	50	45.3	112,504	57	50.7
Fall River, Mass.	111,963	52	46.4	115,428	59	50.8
Richmond, Va.	223,788	106	47.4	193,042	130	67.5
Tampa, Fla.	121,830	60	49.2	108,391	65	59.7
Jacksonville, Fla.	199,013	101	50.8	173,065	155	89.4
Albany, N. Y.	134,222	70	52.2	130,577	60	45.7
Chattanooga, Tenn.	130,537	87	66.6	128,163	146	113.7
Sacramento, Cal.	132,040	116	87.9	105,958	103	97.5

many years the most unfavorable tuberculosis death rate among *all* American cities of 100,000 or more, probably because the Mexicans who comprise a large proportion of the city's residents have proved to be more susceptible to tuberculosis than are white people

of most other nationality groups. San Antonio's death rate from tuberculosis is undeniably still high; on the other hand, one must recognize the great progress which has been and is being made in this community.

Other cities listed in table 3 which have registered sizable declines in tuberculosis mortality are Birmingham, Alabama; Denver, Colorado; and Atlanta, Georgia.

It is difficult to determine why one city, Louisville, Kentucky, with a high tuberculosis death rate in the 1939–1941 period, had approximately the same rate eight years later.

Cities of 100,000 to 250,000 population both in 1950 and in 1940: During the three-year period 1947–1949, tuberculosis mortality in 50 cities with a population of 100,000 to 250,000

TABLE 6

TUBERCULOSIS MORTALITY AMONG RESIDENTS OF CITIES WITH 100,000 POPULATION IN 1950 BUT LESS THAN 100,000 IN 1940; UNITED STATES, 1947–1949 AND 1939–1941*

CITY	1947–1949			1939–1941*		
	Estimated population July 1, 1948	Tuberculosis deaths		1940 population	Tuberculosis deaths	
		Average annual number	Average annual rate		Average annual number	Average annual rate
Total	1,658,206	690	41.6	1,241,871	1,018	82.0
Baton Rouge, La.	109,720	20	18.2	34,719	28	80.6
Berkeley, Cal.	108,860	20	18.4	85,547	21	24.5
Pasadena, Cal.	100,602	24	23.9	81,864	29	35.4
Evansville, Ind.	123,111	31	25.2	97,062	49	50.5
Waterbury, Conn.	103,573	27	26.1	99,314	40	40.3
Shreveport, La.	122,124	34	27.8	98,167	55	56.0
Allentown, Pa.	105,032	30	28.6	96,904	42	43.3
Mobile, Ala.	120,208	50	41.6	78,720	50	63.5
Montgomery, Ala.	101,548	48	47.3	78,084	59	75.6
Corpus Christi, Tex.	99,364	48	48.3	57,301	46	80.3
Savannah, Ga.	115,501	58	50.2	95,996	83	86.5
El Paso, Texas	124,592	65	52.2	96,810	156	161.1
Austin, Texas	124,666	66	52.9	87,930	87	98.9
Little Rock, Ark.	99,733	53	53.1	88,039	83	94.3
Phoenix, Ariz.	99,572	116	116.5	65,414	190	290.5

* Since these cities had less than 100,000 population in 1940, they were not included in Mrs. Liveright's article published July 21, 1944, in *Public Health Reports*. Mortality data are taken from *Vital Statistics Volumes* published by the National Office of Vital Statistics.

both in 1950 and in 1940 averaged 31.6 per 100,000; the death rate for these cities eight years earlier was 46.5. In other words, mortality for these cities as a group declined 32.0 per cent between the two periods (table 5).

Among these urban communities with 100,000 to 250,000 population, the lowest death rate for 1947–1949 was 11.3 in Wichita, Kansas, and the highest 87.9 in Sacramento, California. This extremely high rate in Sacramento is usually attributed to the fact that the city has a large Mexican population; moreover, the city is located in the center of the Sacramento Valley where large numbers of migrant agricultural workers are employed. Many of these migrant workers who are predominantly elderly men, some of them homeless, have a tendency to remain indefinitely in Sacramento. The relationship of elderly

men of indeterminate economic status to a high tuberculosis death rate has long been established.

Cities of this group which have registered a decline in tuberculosis mortality of 50 per cent or more since 1939–1941 are Charlotte, North Carolina; Tulsa, Oklahoma; Norfolk, Virginia; Wichita, Kansas; and Duluth, Minnesota. On the other hand, the tuberculosis death rates have increased slightly in Grand Rapids, Michigan, and in Hartford, Connecticut; a more noticeable increase in Albany, New York, results in a rather high rate for this city, the reason for which is problematical.

Generally speaking, population increases for the cities in this category during the past decade have not been strikingly large. In fact, seven cities of this group had declines in population between 1940 and 1950; these cities were Providence, Rhode Island; Paterson, New Jersey; Scranton, Pennsylvania; Fall River, Massachusetts; Wilmington, Delaware; Reading, Pennsylvania; and New Bedford, Massachusetts.

Cities of 100,000 population or more in 1950 but less in 1940: The 15 cities which reached the 100,000 mark for the first time in the Census of 1950 had average tuberculosis death rates of 41.6 in 1947–1949, compared with 82.0 eight years earlier. According to table 6, an even greater range in tuberculosis mortality[2] is noted among these cities than among those previously studied.

Between 1940 and 1950 the population growth in these cities as a group was 40.6 per cent, while five of the cities registered increases of more than 50 per cent. In other words, some communities in this particular group have been undergoing growing pains while attaining the status of big cities. Sudden population increases of such dimensions often lead, at least temporarily, to chaotic living conditions and allied problems which cause one to expect comparatively high mortality.

Eight of these 15 cities have sizable Negro groups and at least two have large numbers of Spanish-speaking residents among whom tuberculosis mortality is inclined to be quite high.

Baton Rouge, Louisiana, with a tuberculosis death rate of 18.2 per 100,000 population in 1947–1949, had the lowest mortality among the 15 cities; this rate compares with 80.6 in 1939–1941. The phenomenal drop in mortality of 77 per cent seems even more remarkable in view of the fact that Baton Rouge's population increased 216 per cent between 1940 and 1950, making it the fastest growing city in the United States. In the face of this sudden transition, one would expect a much higher tuberculosis death rate than that recorded for the recent three-year period; apparently some unknown factors are at work.

The highest tuberculosis mortality among cities of this group was found in Phoenix, Arizona; in this city, long known as a mecca for cure seekers, the average tuberculosis death rate among residents was 116.5 in 1947–1949, compared with 290.5 eight years earlier. Although the more recent rate is still extremely high, the city is to be congratulated on this 60 per cent decline over an eight-year period. Between 1940 and 1950 the population of Phoenix increased 63 per cent.

Another city with a pronounced decline in tuberculosis mortality is El Paso, Texas, where the rate dropped from 161.1 in the earlier period to 52.2 in 1947–1949.

Because of the comparatively small population figures for this particular group of cities, death rates are undoubtedly more subject to chance fluctuation than is true with communities of greater size.

All cities of 100,000 population or more in 1950: Of the 106 American cities with more

[2] Since these cities had less than 100,000 population in 1940, they were not included in Mrs. Liveright's article published July 21, 1944, in *Public Health Reports*. Mortality data are taken from *Vital Statistics Volumes* published by the National Office of Vital Statistics.

than 100,000 population in 1950, the one with the lowest tuberculosis mortality in 1947–1949 was Wichita, Kansas; this city had an average rate of 11.3 per 100,000, while Salt Lake City, Utah, with a rate of 11.9, was a close second.

Largely due to abnormal circumstances, Phoenix, Arizona, had the highest tuberculosis death rate among the 106 cities; in this city the residents—many of them cure seekers—had a rate of 116.5 during the recent period studied. Sacramento, with a rate of 87.9 per 100,000, had the next highest mortality from this preventable disease.

December, 1951 MARY DEMPSEY

NOTES

THE LAENNEC SOCIETY OF PHILADELPHIA

The Laennec Society of Philadelphia awards an annual prize of $200.00 for the best paper submitted in any field related to diseases of the chest. This prize is open to undergraduates, interns, residents, or Fellows throughout the United States. The work should be original and not a review of literature or of previous contributions. The Society does not reserve the right of publication but requests that the prize-winning paper be presented at one of its regular scientific meetings.

Five copies of the manuscript should be submitted in the customary form for publication, i.e., double-spaced and with wide margins. They should be in the hands of the Secretary of the Society, Dr. Charles M. Norris, 3401 North Broad Street, Philadelphia 40, Pennsylvania, by October 1, 1952.

POSTGRADUATE COURSE IN TUBERCULOSIS

October 21–24, 1952

The National Sanitarium Association is arranging a four-day postgraduate course in tuberculosis for physicians and surgeons to be held for three days at the Toronto Hospital for Tuberculosis, Weston, Ontario, with an additional day to include the program for the Annual Meeting of the Ontario Laennec Society to be held at the Royal York Hotel, Toronto.

Subjects to be considered will include advanced knowledge of the bacteriology and pathology of tuberculosis, epidemiology, differential diagnosis of pulmonary and other forms of tuberculosis, the medical and surgical treatment of the usual forms of tuberculosis encountered by physicians and surgeons engaged in sanatorium practice, private practice in internal medicine, thoracic, orthopedic, and genitourinary surgery, as well as in public health and allied fields.

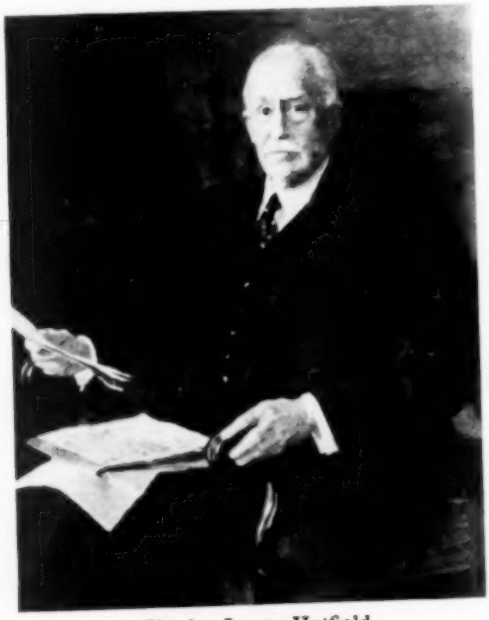
Further particulars can be obtained by writing to the Medical Superintendent, Toronto Hospital for Tuberculosis, Weston, Ontario.

Obituaries

CHARLES JAMES HATFIELD

1867–1951

Dr. Charles Hatfield had, following his return from his studies in Europe in 1902, served on the staff of White Haven Sanatorium and The Henry Phipps Institute and, because of his outstanding abilities, was selected as chairman of the all-important committee on Exhibits and Prizes at the meeting of the International Conference on Tuberculosis in



Charles James Hatfield

Washington in 1908. There he had to deal with such questions as where exhibits should be placed, why others had not arrived, how to locate lost articles, et cetera. One could hardly imagine a more trying situation, and his ability, his quiet dignity, and his unfailing courtesy made a great impression. Few ever knew that in order to fulfill the assignment given him he was forced to miss, not only the Philadelphia Conference, but also all the sessions of the Congress and all of the social functions, with the opportunity of meeting the great leaders in the work from abroad.

This was typical of the man, for Charles Hatfield had an extraordinarily well-developed sense of his responsibilities: to his family, his church, his friends, and his work. Through his long life he held faithfully to his principles.

The tragic death of his wife left him with three small children, and his constant thought was to give them all that she would have wished for them in matters of health, education, travel, and social contacts. Throughout the eight years that he was Managing Director of the National Tuberculosis Association he commuted from Philadelphia to New York and, when his work took him around the country, he phoned his home daily, and took the first train home once his work was done. He took special pride in the development of the excellent Community Nursing Center at his summer home in Keene Valley, New York, because it had been one of his wife's especial interests.

He was a man who regarded his services to his church as a privilege rather than an obligation, and was a devout supporter of the Presbyterian Church at Chestnut Hill and of the Congregational Church in Keene Valley.

He was punctilious in observance of his social obligations. He loved nothing better after a hard day's work than to relax at dinner and a game of "contract" with a group of friends. His quiet dignity, his personal charm, and his wide knowledge of men and affairs made him alike a charming host or an always welcome guest.

His health work in many fields brought him in contact with men of conflicting opinions and into discussions that tended at times to become acrimonious, but never so on his part. His unfailing courtesy never abated. After one rather trying meeting of an Executive Committee, one member who had been vociferously opposing him said: "I think I could get to love that man Hatfield; he is such a gentleman! "

A mere listing of the organizations which he served gives ample testimony to his powerful influence on the development of the health work of his state and nation. He joined the staff of The Henry Phipps Institute in 1903, and wrote the history of the first patient treated there. He was its Executive Director from 1912 to 1935 and Associate Director until 1947, serving as Acting Director during the absence of Dr. Long in Army Service. He was on the Board of the Pennsylvania Tuberculosis Society from 1904 to 1948 and was its President, 1907–1910, a founder of the Philadelphia Tuberculosis and Health Association and its President, 1923–1947. He had been a Life Trustee of the University of Pennsylvania since 1921 and for many years Chairman of its Committee on Graduate Medical Education and Research, Chairman for South Eastern Pennsylvania of the American Red Cross 1919–1927, Chairman, Health Department, Philadelphia Council of Social Agencies 1938–1945, organizer of the Potts Memorial Institute (for rehabilitation of ex-sanatorium patients) at Livingston, New York, and its President 1926–1948.

Prior to World War I, the International Tuberculosis Association had its headquarters in Berlin, and its activities were directed from there. In 1919 the British held a conference on public health in London. They asked the French and ourselves to send delegates to discuss the re-establishment of an international tuberculosis association. The British were represented by Sir Robert Philip, of Edinburgh; Dr. Nathan Raw, of Liverpool; Dr. Menzies, Health Officer of London; Miss McGaw, Secretary of the British Association; and others. France sent Dr. Edouard Rist and Dr. Leon Bernard, Minister of Health. Our delegates were Dr. Hatfield and Dr. David Lyman. In the discussions in London and later in Paris, where further conferences were held with leading workers in France, Dr. Hatfield's executive ability contributed greatly to the organization of the International Union as it is today. He was the delegate and speaker for the United States at its Lisbon meeting in 1937.

His greatest contribution, however, was to the National Tuberculosis Association. He was one of the group who founded it in 1904, served on its Executive Committee for many years, was Managing Director 1914–1922, President 1924–1925, Trudeau Medalist 1927, and Secretary 1927–1948.

Under his regime as Managing Director, the National Tuberculosis Association started the first nationwide effort to promote health education in the schools, preparing textbooks on health education and distributing them to the schools. It organized "The Modern Health Crusaders," children in the schools practicing simple rules of personal hygiene on a competitive basis before any of the organizations devoted to child welfare had developed a national program; and was a prime mover in the formation of the National Council of Health Agencies. Under his influence the Association established the Committee on Research which has played such an outstanding part in the program over the past thirty years and carried through the reorganization of the National Association that has made it one of the most efficient as well as one of the greatest national health associations in the world.

Kipling cites as one of the qualifications of a *man* the ability to

> "force your heart and nerve and sinew
> To serve your turn long after they are gone,
> And so hold on when there is nothing in you
> Except the WILL which says to them 'Hold on'!"

In his last years, when his mind was becoming clouded, only the older group who had worked with him and loved him realized that his lifelong sense of obligation to his work had outlasted his ability to contribute to its counsels.

Few indeed are the men who have done so much for the development of the National Association or done so with such quiet efficiency and complete unselfishness.

WILL ROSS

1888–1951

Will Ross was one of the heroes of our generation. The story of his life has been a joy and an inspiration to many. It is not possible to estimate the influence which he has had on the health and happiness of others and on the forward progress of tuberculosis control.

Stricken with tuberculosis during the most productive years of life, he not only succeeded in attaining an almost miraculous recovery but made a success of rehabilitation which will serve as an inspiring example as long as tales are told. He then devoted himself faithfully to prevent tuberculosis in others, eventually becoming the President of the National Tuberculosis Association, one of the few laymen ever to attain that honor. His presidential address was an inspired appeal.

Will Ross was born in Appleton, Wisconsin, in 1888. His parents moved into a home where a former tuberculous patient had lived. At an early age, the youngster crawled over rugs and carpets and household effects which had remained in this house. It is thought that this may have been responsible for the development of the tuberculosis which exploded in his high school days. Like many others, he tried outdoor living in the Southwest, but his health steadily failed, and he returned to Wisconsin and entered River Pines Sanatorium. He expected to stay a week, but remained for five years.

During his later years as a patient, he did part-time office work and then started a small "canteen" for patients. This he gradually expanded until 1919, when he removed the business to two small rooms in Milwaukee. Growth was continuous and today Will Ross, Inc., is one of the larger and better known hospital supply houses.

Will Ross always found time and energy enough to work hard in tuberculosis prevention. He was one of the builders of the Wisconsin Anti-Tuberculosis Association. His work

broadened to the Mississippi Valley Conference where he was honored by receiving the Dearholt Medal.

He had served on the Board and on committees of the National Tuberculosis Association since 1938. He was always a driving force for accomplishment of whatever was best for the tuberculous patient and for the prevention of the disease. He was President of the National Tuberculosis Association in 1945–46, the second of two nonmedical presidents.

Will Ross

Civic activities at home also attracted his attention. In 1942 he was general chairman of the Community War Fund Campaign, and he gave service on the boards of the Young Men's Christian Association, Curative Work Shop, American Red Cross, Marquette University School of Medicine, and the Metropolitan Milwaukee War Memorial.

The world has been made a better place because of the life of Will Ross.

ESTHER ROSENCRANTZ

1876–1950

Dr. Rosencrantz, long a diligent and enthusiastic worker in tuberculosis and long a member of the American Trudeau Society, died on December 17, 1950. Dr. Rosen-

crantz was a graduate of Stanford and Johns Hopkins Universities and studied extensively in England, Germany, France, and Switzerland, returning thereafter to her native California where she became identified with the University of California in San Francisco, finally as Associate Professor of Medicine. Her work with the Red Cross Commission after the First World War won decorations by the Italian and American governments.

Possessed of unusual scientific zeal and interest, she made excursions into numerous fields of medicine to which she contributed substantially, but tuberculosis and the Tuberculosis Clinic in the San Francisco Hospital were the outlets for most of her constructive work.

Her sparkling personality, her devotion to work, and the enthusiasm with which she approached her responsibilities endeared her to many, both inside and outside the profession she passionately loved.

GEORGE C. STUCKY

1888–1951

Eight years as Superintendent of Ingham County Sanatorium and eighteen years as Medical Director of Eaton County Health Department, Michigan, represents Dr. George C. Stucky's period of active contribution to the health of his state. He was late in completing his medical training because tuberculosis in his family interrupted his schooling and took him to Saranac Lake where he spent several years as technician in Saranac Lake Laboratory. His graduation in medicine in 1923 from the University of Michigan was followed by an internship at the Henry Ford Hospital, from which he entered upon his duties just enumerated. Dr. Stucky was born May 10, 1888, in Louisville, Kentucky.

His ear was attuned to the needs which tuberculosis and inadequate general health organization impose upon the public and he gave much effort and thought to improving the health of his fellow man. He had been a member of the Board of Directors of the National Tuberculosis Association and a member of the American Trudeau Society. In countless ways he contributed helpfully to the work of the Michigan Tuberculosis Association. He was a member of the American College of Physicians, was certified by the American Board of Preventive Medicine and Public Health, and was lecturer in the University of Michigan School of Public Health, Ann Arbor. He had been president of the Michigan Health Officers' Association, Michigan Trudeau Society, and Michigan Sanatorium Association.

His concern for others was a highly developed attribute of his life. His death on November 26, 1951, takes a leader from the health crusade of his state and a wise and valued friend from those who knew him.

EDWARD JAMES ROGERS

1877–1951

Dr. Edward James Rogers, son of a confederate soldier who was one of Morgan's command during the Civil War, was Superintendent and Medical Director of the Vermont State Sanatorium from 1913 until his retirement in 1947. There he directed the lives of countless patients with sympathy and skill. He was a member of the State Board of Health from 1923–1931, acting as Chairman of the Board from 1925–1930. At the time of his retirement he was also Medical Director of the Caverly Preventorium at Pittsford and the Washington County Sanatorium at Barre.

Dr. Rogers was born in the historical town of Ninety-Six, South Carolina, January 7,

1877. He was educated at the Citadel, the Military College of South Carolina, and received his medical degree from the Medical College of the State of South Carolina in 1908. Following graduation, he was resident physician at Loomis Sanatorium Annex, Liberty, New York, from 1908 to 1911. He then entered the College of Physicians and Surgeons of Columbia University, New York, and received another medical degree in 1912.

Dr. Rogers was a physician in the finest sense of the word, and the people of Vermont have lost not only a physician but a friend.

JOHN NANTS WILSON

1900–1951

Dr. John Nants Wilson, Assistant Chief of the Tuberculosis Division at the Washington Central Office of the Veterans Administration since 1948, died November 3, 1951 at Mt. Alto Hospital, Washington, D. C., after an illness of twelve days. He was buried at Arlington Cemetery.

Dr. Wilson had been with the Veterans Administration in various capacities for twenty-two years. In 1929 he entered Veterans Administration Tuberculosis Service at Rutland Heights, Massachusetts, serving there until called to the Central Office as Medical Advisor to the Insurance Claims Service in 1940. Appointed to the Managership of the Rutland Heights Hospital in 1945, he served there for three years during which time, in cooperation with the state and local tuberculosis associations, he helped develop a program of patient education.

His paper, "Methods Used to Improve Hospital Facilities," was given before the National Tuberculosis Association's 50th Annual Meeting in New York in 1948. In 1949 he was a member of the Committee on the Revision of Diagnostic Standards of the National Tuberculosis Association.

Dr. Wilson was born in Landover, Maryland, in 1900. During World War I, he served in France as a corporal in the U. S. Marine Corps. He earned his medical degree at George Washington University and interned at the University Hospital. For a brief time he was resident physician at St. Elizabeth's Hospital in Washington.

In addition to membership in the National Tuberculosis Association, Dr. Wilson was a Fellow of the American Medical Association and the American College of Chest Physicians.

SETH COX

1881–1952

Dr. Cox was born in Illinois, November 20, 1881. He received his medical degree from Jefferson School of Medicine in 1912, and practiced in Topeka, Kansas, until a short time before he moved to Seattle, Washington, where he died of angina pectoris on February 26, 1952.

He was a Fellow in the American Medical Association, a member of the American Trudeau Society, and was qualified in pulmonary disease.

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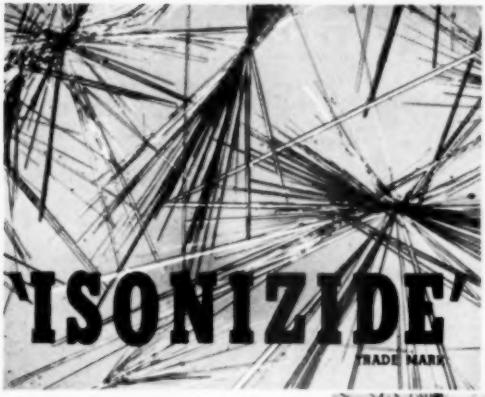

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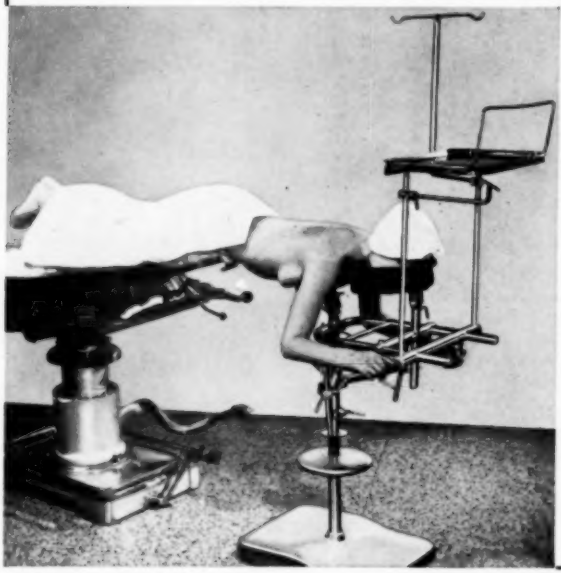

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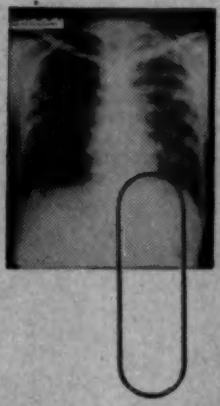

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